NON-QUOAD GOITRE

STUDIES IN ITS AETIOLOGY AND DIAGNOSIS

by

JAMES ANTHONY BOYLE

M.B. Ch.B. (Glasg.),

M.R.C.P.(Ed.),

M.R.C.P. (Lond.).

PREFACE

This thesis describes some studies in the aetiology and diagnosis of non-toxic goitre and is in three parts.

The first part concerns an investigation into the role of hereditary factors and environmental factors (namely iodine deficiency) in the production of simple goitre. In this study a large twin sample was screened for the presence or absence of simple goitre and plasma inorganic iodine (PII) levels were determined in the majority of the twins by a recently described technique of PII measurement which I have validated in a preliminary section of this part of the thesis. The twin-study method allowed an appraisal of the role of heredity in simple goitre formation.

The second part of the thesis describes a study of the phenomenon of iodide inhibition in thyroid disease and the usefulness of this technique to the clinician in the diagnosis of Hashimoto's disease from simple goitre and simple goitre from toxic goitre. I have extended my observations to the study of the phenomenon in other thyroid states and my findings are described in this part of the thesis, together with some work which suggests some possible mechanisms of occurrence of iodide inhibition in various states of thyroid function.

The third part deals with the use of probability theory/

theory in the differential diagnosis of the non-toxic goitre. The theory of conditional probability was first clearly enunciated by Bayes in 1763 and later by Laplace in 1791; insofar as its application to the problem of diagnosis of non-toxic goitre was concerned however it was a new technique which seemed worthy of study. An automatic electronic digital computer was used to calculate the probabilities of diagnoses for the 3 conditions Hashimoto's disease, simple goitre and thyroid cancer for a large series of patients and the results have been compared with the unconscious but effective assessment of probabilities of disease occurrence made by experienced clinicians.

To make the reading of the thesis easier, all of the tables are presented in Volume 2 and the page number where any table can be found in Volume 2 is quoted each time the table is mentioned in Volume 1. Separate Summaries are presented at the conclusion of each section of each part and these Summaries have been indexed in the table of contents. The references to each section appear at the end of that section and are also indexed in the table of contents. Furthermore the first table or figure or appendix in any section is known as Table 1 or Figure 1 or Appendix A irrespective of where the section appears in the thesis. This should not cause confusion because the tables and Appendices have page reference numbers after them showing where they can be located in Volume 2.

ACKNOWLEDGEMENTS

The work on which this thesis is based was undertaken during the period 1963 - 1966 when I was Hall Tutorial Fellow in Medicine and then Registrar in Medicine in the University Department of Medicine, Royal Infirmary, Glasgow. It describes observations which I made on over 750 subjects in studies of the aetiology and diagnosis of non-toxic goitre.

I should like to express my gratitude to the following. Sir Edward Wayne for first arousing my interest in the thyroid gland when I was his House Physician and more especially for stimulating me to think in terms of ascribing numerical values to symptoms and signs in arriving at a diagnosis. I am grateful to Professor E.M. McGirr for fostering this interest and allowing me ample facilities for research and experiment in his wards and laboratories and also for his constructive and mature criticism. I am grateful to my colleagues at the Thyroid Clinic, Royal Infirmary, Glasgow, for their generous help in the clinical aspects of this thesis especially Part 3. I thank Miss J. Nicol and Miss M. Gray for technical assistance in the estimation of /

of urine iodine and urine and plasma creatinine in Part 1. I should also like to thank the twins in the City of Glasgow and the West of Scotland who by their generous co-operation made possible the study reported in Part 1 of the thesis. I acknowledge my indebtedness to the librarians of the following colleges and institutions: Royal College of Physicians and Surgeons, Glasgow, The University of Glasgow, The Royal College of Physicians of London, The British Medical Association, The Royal Society of Medicine and H.M. Patent Office. Finally, I should like to thank Miss I. Dickson and Mrs. M. Skene for typing the MS.

Some of the work in this thesis has been published or accepted for publication in the following Journals:

"A comparison of two methods of plasma inorganic iodine estimation in euthyroid goitrous and hyperthyroid subjects". J. Clin. Endocr. 25, 1035. 1965 with A. Sloss, E. Macdonald and M. Gray.

"Clinical and Radiobiological Observations on Latent effects of X-irradiation on the thyroid gland". J. Clin. Endocr. 25, 1009 (1965) with W.R. Greig, S. Fulton and W.W. Buchanan.

"The phenomenon of iodide inhibition in various states of thyroid function with observations on one mechanism of its occurrence". J. Clin. Endocr. 25, 1255. (1965) with J.A. Thomson, I.P.C. Murray, S. Fulton, J. Nicol and E.M. McGirr.

"Application des Calculateurs dans le diagnostic du Goitre non-toxique". Proc. Congres Internationale sur l'Informatique. Toulouse, March, 1966 (In press). (By invitation).

"Construction of a model for Computer-assisted diagnosis: application to the problem of non-toxic goitre." Quart. J. Med. (accepted for publication) with W.R. Greig, D.A. Franklin, R. McG. Harden, W.W. Buchanan and E.M. McGirr.

"Computer assisted diagnosis of non-toxic goitre".
Proc. Royal Festival Hall Symposium on 'Progress in Medical Computing, June, 1965. London. (By invitation)

"An experimental approach to the calculation of diagnosis using an automatic digital computer."
Proc. Western Regional Hospital Board Symposium on 'Medical Computing', Glasgow, November, 1965. (By invitation)

"Genetic and environmental factors in the aetiology of simple goitre: data from a twin study". Quart. J. Med. (in press)
With W. R. Greig, M. Gray, J. Nicol, W. W. Buchanan, A. Duncan and E. M. McGirr.

I have been awarded the Alexander Fletcher Memorial Prize Lecture, Royal College of Physicians and Surgeons of Glasgow, to be given in January, 1967 on the basis of some of the observations in this Thesis. The title of the Lecture will be "The application of the twin study method to some problems in clinical genetics".

I have personally presented some of the data in the thesis at the following meetings:

"The phenomenon of iodide inhibition in various states of thyroid function" V Int. Thyroid Conference, Rome 1965, Section III C.

"Symposium on "Balance and Dynamics of Iodine in Iodine Deficiency and in Physiological Conditions", under the aegis of Euration, Brussels, June, 1965."
Title "The Kinetics of Iodide Inhibition". (By invitation).

"Congres Internationale sur l'Informatique."
Toulouse, March, 1966.
Title " Application des Calculateurs dans le Diagnostic du Goitre Non-Toxique". (Proceedings in Press). (By invitation).

"Ninth International Congress of the Society of Internal Medicine. Section: Recent Advances in Internal Medicine.
Amsterdam, September, 1966.
Title: "Further experience with Computer-assisted diagnosis."
(Proceedings to be published). (By invitation).

"A Study of the Role of Iodine Deficiency in Simple Goitre in the Glasgow Area."
Nutrition Society 180th Meeting, London, May, 1966.

TABLE OF CONTENTS

References/

Page

PART 2

The phenomenon of iodide inhibition

PART 3

PART 1

SECTION 1

THE AETIOLOGY OF SIMPLE GOITRE

(A REVIEW)

"Quis tumidum guttur miratur in Alpibus?" * sang the poet Juvenal almost two thousand years ago (1). This has not turned out the majority opinion for simple endemic goitre to which Juvenal was clearly referring has provoked a great deal of wonder and this wonder has been the cause of many detailed studies and investigations. In this introduction I shall attempt to describe briefly some of these studies and investigations, and also to show why these are still areas where in spite of this, there is cause for wonder. This introduction must be incomplete because a full account of the work which has been done on simple goitre, both sporadic and endemic, would fill many volumes.

Goitre has probably been present for many thousands of years. Popovitch (2) in his article "The history of goitre study according to materials of Chinese domestic medicine", refers to the legendary Chinese Emperor Shen-Nung (2839 - 2698 BC) who in his book Pen - Ts' ao Tsing, which describes the therapeutic value of herbs mentions the iodine - containing seaweed Sargassum as a cure for goitre and/

* " Who wonders at a swollen throat in the Alps?"

and Jantsch (3) quotes other references to Shen - Nung's goitre treatment. The Ancient Hindu literature contains references to goitre in spells for protection against goitre which are found in the Artharva - Veda (4). Susruta and Chakrata two early Hindu physicians who lived about 400 BC gave the name "galganda" to tumours of the neck and there is general agreement that these tumours are likely to have been goitres (5). In the Ebers Papyrus (6,7) we read that tumours of the neck which occurred in Ancient Egypt were treated surgically and Mettler (8) in her book on the history of medicine is of the opinion that these operations were in reality thyroidectomies for goitre.

Wilson (9) has defined simple goitre as visible and palpable enlargement which is not the consequence of auto-immune thyroiditis, neoplasm, including the benign solitary adenoma, goitrogen administration, thyrotoxicosis or currently recognised defects in thyroid hormone synthesis. Hubble (10) has remarked that there are no simple goitres only simple people who think that these goitres are simple. This comment does pinpoint the fact that from what is now known about simple goitre, its nature and aetiology are much more likely to be complex than simple.

If simple goitre were possibly widespread in the old world/

world it is certainly so in the new. Its incidence differs from country to country, region to region, village to village (11). In certain areas where 10 per cent of the population are affected goitre is said to be endemic (12), and simple goitre has been reported as endemic in some area of almost every country in the world. As Kelly and Snedden (11) have remarked, "goitre ..... occurs with varying intensity in almost every country .....". The disease has been observed in the far north, in the tropics and in the far south; it occurs independently of climate, season or weather. Moreover in its incidence goitre makes no distinction of race, nationality, colour, creed or class; the North American, the European, the Chinese, the Himalayan Indian, the Turkoman, and the peoples of Central and South America all suffer from it under certain conditions - some severely, some moderately, some but mildly". These authors give fascinating accounts of the world wide occurrence of simple goitre in endemic form (11). Other excellent accounts are given by the WHO Chronicle, the Chilean Iodine Educational Bureau and Greenwald (13 - 15).

Before discussing the aetiology of simple goitre it is probably/

probably worth while making two general points. Firstly it is unlikely that there is one sole cause of simple goitre. It is much more probable that, as with many situations in medicine or in life, there are multiple factors involved. Greenwald (16) has commented that it is possible that goitre has been ascribed to a greater variety of causes than any other disease. He goes on to remark that one of the chief factors responsible for this is "the readiness of those who have discussed the subject to fasten on some local peculiarity as the cause of the disease." In 1933 McCarrison who had spent a lifetime on goitre research in the Ganges basin in India was able to say, "It is evident ..... that the causes of goitre are multiple and their effects manifold ..... and that their combination in various ways may give rise in different persons and in different localities to different types of goitre both of a sporadic and an endemic kind" (17).

The second general comment is that aetiological factors which have been shown experimentally to affect thyroid hypertrophy must not be regarded as the only ones involved in human pathology as has been discussed by Roche and Lissitzky (18).

The function of the thyroid gland is to concentrate iodide from the blood, to synthesise thyroid hormone and release it into the circulation. The activity of the thyroid is controlled/

controlled by thyrotrophic hormone (T.S.H.) which is secreted by the anterior pituitary gland. The rate of secretion of T.S.H. is controlled by the level of thyroid hormone in the plasma and when this level falls for any reason an increased secretion of T.S.H. ensues causing increased thyroid activity. Should there be a permanent falling off in thyroid activity this results in prolonged T.S.H. secretion which causes hypertrophy and hyperplasia of the gland. These changes are initially at least compensatory processes (19) and both of them contribute to an increase in the weight of the gland (20) causing goitre.

Simple goitres may be either diffuse or nodular and although Taylor (21) has shown that nodules appear in a goitre with the evolution of time and are thus found more commonly in older glands the precise mechanism responsible for their appearance is not fully understood. One widely held view is that the thyroid gland may eventually become exhausted by continued T.S.H. stimulation and hyperplasia and hypertrophy then regress giving way to colloid filled vesicles with the epithelium in resting state (18). Some writers however do not wholly accept the view that simple goitre is a T.S.H. produced enlargement which compensates for difficulty in thyroid hormone synthesis. Trotter (22) has suggested/

suggested that simple goitre might be the result of an unidentified stimulus to thyroid growth not mediated by T.S.H.

I shall now discuss some of the factors which have been suggested or shown to be implicated in the aetiology of goitre.

Iodine Deficiency

The evidence that iodine deficiency is implicated in the aetiology of simple endemic goitre is overwhelming and rests on the following points.

Firstly simple endemic goitre has been shown to have the highest prevalence in areas where the iodine content of the water, soil, salt and food is lowest. The French chemist Chatin (23) was probably the first to show this after we had determined the concentration of iodine in air, water, soils and animal and vegetable foods in various localities in France. He found that these areas could be divided into four zones in which the incidence of goitre was inversely proportional to the iodine content of the environment. On the basis of these findings, Chatin stated his conclusions as follows "Le goître et le crétinisme sont inconnus dans les contrées normalement iodurées. Les maladies se montrent quand la proportion d'iode diminue". Subsequent investigators (24)/

(24) failed to confirm Chatin's observations, possibly because of the difficulties involved in the micro-determination of the iodine content of natural substances and his findings fall into disrepute. Seventy years later however his studies received due recognition when his work was repeated and confirmed in Switzerland (25) and the U.S.A. (26).

Secondly the administration of iodine to populations has dramatically reduced the prevalence of simple endemic goitre in many areas. The first experiment in goitre prophylaxis ever known was carried out in France in the departments of Bas-Rhin, Seine-Inférieure and Haute - Savoie (27). The amount of iodine administered to the schoolchildren in this area was so large that iodism and Jod-Basedow were frequent and the experiment was discredited and abandoned (28). The true foundation of iodine prophylaxis of simple endemic goitre was laid by the observations of Marine and Kimball in Akron, Ohio, U.S.A. (29 - 31) when they showed in a study of about 5000 girls between the ages of 11 to 18 years that 4.0 g sodium iodide a year produced a considerable decrease in goitre size in over 60 per cent of the treated group. Only 13.8 per cent of the untreated group showed a spontaneous regression of goitre. The findings of this trial, the first controlled study/

study of its kind, have been confirmed many times (32 - 39).

The third piece of evidence implicating iodine deficiency in the causation of simple endemic goitre is that goitrous subjects in endemic goitre areas can be shown by appropriate techniques to have abnormalities of stable and radioiodine metabolism wholly consistent with the concept that their thyroid glands are avid for iodine and that they are iodine deficient. In a careful study of subjects in an endemic area of simple goitre in Mendoza, Western Argentina, Stanbury and his colleagues (40) found that goitrous patients had a low urinary excretion of stable iodine and a high thyroid avidity for ^{131}I whereas those patients who had succeeded in obtaining an adequate supply of iodine exhibited thyroidal ^{131}I uptake values which would have been considered normal in non-endemic regions. Previously, Elmer (41) had shown, using a stable isotope of iodine, that the uptake of stable iodine by the thyroid of a patient with endemic goitre is greater than normal and this observation has been confirmed many times in various areas endemic for simple goitre (40,42 - 45).

Lastly/

Lastly some workers (46 - 47) have been able to produce goitre in experimental animals fed on an iodine deficient diet. The argument that simple endemic goitre is caused by iodine deficiency is therefore soundly based and the evidence on which it is founded is impressive. However as early as 1935 it was shown that in some endemic goitre areas there is scanty evidence of iodine deficiency (48) and as Greenwald (49) has pointed out at least three different workers have failed to produce goitre in animals maintained on purified diets low in iodine. Recently Dimitriadou and her colleagues have met with similar lack of success in producing goitre in rats maintained on an iodine deficient diet for many months (50). The iodine content of the endemic goitre varies widely and although the concentration is usually lower than normal the total amount of iodine in the gland is sometimes greater than normal (51). One author has commented that it seems likely that the thyroid enlargement could not in these circumstances have been due to a lack of iodine in the customary food (52). Furthermore not all persons living in area of simple goitre endemicity where the iodine content of water and soil is low, develop goitre.

A/

A recent study by Malamos et al (53) in Greece demonstrates this and shows in addition that there was no difference in iodine metabolism between goitrous and non-goitrous persons: iodine deficiency patterns of ^{131}I kinetics were observed in both groups. Similar findings have been reported by Roche (54). All of these facts argue against iodine deficiency being the sole cause of goitre even in areas of iodine lack. Malamos et al. concluded from their study that a "host" factor must be present in addition to iodine deficiency for goitre to appear. In addition, classical iodine deficiency goitre can regress spontaneously as is shown by the experience of Hood (36) who found that during the years 1923 to 1928 the incidence of goitre in Swiss recruits dropped spontaneously from 51.8 per cent to 13.5 per cent. This was attributed to a supposed improvement in the drinking water and general level of hygiene. After the introduction of iodised salt however the goitre rate fell to almost zero. Finally apart from outbreaks of endemic goitre caused by goitrogens (described later) it is now being increasingly realised that in some endemic goitre areas there is no lack of iodine in the environment (55). In Eastern Kentucky, London and his associates have described an extremely interesting situation: endemic simple goitre/

goitre in an area which was not iodine deficient where the uptake of stable iodine by the goitrous thyroid is high (56); and in Mexico, Vought et al (57) have studied goitrous children who were in positive iodine balance, but had low levels of inorganic iodine in the plasma. One possible explanation which suggested itself to these workers for their results was that the positive iodine balance and low levels of inorganic iodine in the plasma were the consequence of the goitre rather than the evidence of dietary iodine deficiency.

It might reasonably be concluded from the work reviewed so far that gross iodine deficiency is often associated with the occurrence of endemic goitre and that it may act with other as yet undetermined factors to produce goitre; that iodine prophylaxis is of the utmost value in the prevention of goitre and that a few areas exist where simple goitre is endemic and iodine deficiency is not a causal agent.

Recently there has been growing evidence of low levels of inorganic iodine in the plasma of patients with sporadic goitre. This was first suggested by the work of Wayne and his colleagues who studied the dietary intake of iodine, the pasma inorganic iodine levels (PII) and the uptake of stable iodine by the thyroid gland in unit time (AIU) in patients with simple goitre and in control subjects/

subjects (58 - 60). They found that patients with simple goitre could be divided into two groups: those with increased thyroidal avidity for iodine (demonstrated by high thyroidal radioiodine clearance rates) and those whose thyroid glands were not unduly avid for iodine (shown by a normal radioiodine clearance rate). Those patients with high thyroidal radioiodine clearance rates had lower PII levels and lower dietary intakes of iodine (usually due to dietary idiosyncrasy against fish) than did controls. Patients with a normal radioiodine clearance rate had values for PII and AIU which fell midway between these two groups. In addition renal excretion of stable iodine was significantly lower in all patients with simple goitre than in the controls. Other workers have also found a low PII level in some patients with simple sporadic goitre (61 - 63) although de Groot failed to confirm this finding in 4 patients with simple goitre whom he studied (64).

Wayne et al (60) interpreted their findings to mean that a dietary deficiency of iodine arising from idiosyncrasies of diet, mainly in abstinence from fish, leads to a low PII which either by itself or in conjunction with other factors eventually causes goitre. They postulated that because the PII is low, the thyroid gland/

gland had to clear more plasma of its iodine concentration to keep the AIU normal. In so doing thyroid enlargement resulted. Some caution is, however, required in interpreting results of studies of stable iodine metabolism because as Vought and his colleagues (57) have pointed out the low PII could equally well be due to and need not necessarily be the cause of increased thyroidal avidity for iodine. Furthermore not all workers believe that fish supplies most of our dietary intake of iodine. Broadhead et al (65) calculated on the basis of measurement of the iodine content of milk that during the winter months milk would be a much more important source of dietary iodine than fish. If increased thyroidal avidity for iodine were of importance in producing a low PII one might expect a low PII in patients with thyrotoxicosis. and this finding has been reported by some (59,62,63) but not by all (66) workers. (The presence of organic compounds of iodine in the urine in patients with thyrotoxicosis (67) makes accurate assessment of the PII technically difficult and it is likely that the PII levels in thyrotoxicosis are even lower than those whichhave been reported).

It is a reasonable conclusion that the case for dietary iodine deficiency being a causal factor in the development of/

of simple sporadic goitre is not so well proven as it is for simple endemic goitre.

From a theoretical standpoint iodine deficiency could arise not only from dietary lack of iodine but also from excess loss of iodine in the urine, stools or sweat. Cassano et al have studied the renal clearance of iodine in pregnancy and at puberty (68 - 70) and have shown it to be elevated at these times. These workers suggested, on the basis of family studies, that there may be a familial predisposition to develop an increase in renal clearance at these times and this, they considered might account for some cases of simple goitre. Aboul-Khair et al (71) have confirmed the finding of Cassano et al that the renal clearance of iodine is high in pregnancy and have shown a correlation between PII values and urinary loss of iodine. They believe that their findings may account for the development of simple goitre during pregnancy. Losses of iodine in sweat are small (72) and are unlikely to be implicated in the causation of simple goitre. It has been suggested (73) that loss of iodine in the faeces could contribute to and help maintain an iodine deficiency state in some patients with simple goitre.

Goitrogens

Indisputable proof of the existance of dietary goitrogens was first afforded by the work of Chesney et al who made the chance/

chance discovery that rabbits fed on cabbage developed goitre (74). This finding was quickly confirmed by Marine et al (75) and by McCarrison (76) and it was later shown that cyanides which occur in the Genus Brassica (77), Swedes (78) and soya and groundnut seeds (79) were goitrogenic. The goitrogenic substance in Swedes has been shown to be L - 5 - Vinyl - 2 - thio oxazolidone (Goitrin) (80 - 81) which exists in uncooked vegetables as a precursor (progoitrin) (82). Cooking lessens the goitrogenic activity in many foodstuffs possibly by destroying enzymes which convert progoitrin to goitrin (83). Goitrin has an action on thyroid hormone synthesis similar to that of the thiourea derivatives (80). Instances of goitre due to dietary consumption of foods containing goitrin are however rare. The case has been described of a woman (84) ingesting large amounts of Rutabaga (which contains L - 5 - vinyl - 2 - thio oxazolidone) who developed a goitre. During the German occupation of Belgium, an outbreak of simple goitre there was ascribed possibly to the increased consumption of cabbage and vegetables of the Brassica family by the populace (85). Greenwald (86) however disputes that this was the case. Goitre due to the ingestion of milk containing a goitrogen has been demonstrated/

demonstrated in Tasmania (87 - 90) where cows fed on marrowstem kale produced milk in which a substance with goitrogenic action was found. Children who consumed this milk developed goitres which could not be prevented by the administration of 10 mg Potassium iodide weekly. Later it was shown that thiocyanate was present in high concentration in this milk (91). Goitrogenic activity of milk in cattle and in man has been reported from Finland (92,93) the goitrogen being identified as L - 5 - vinyl - 2 - thio oxazolidone and this seems to be a main cause of simple endemic goitre in an area there. Goitrogens in milk have been reported in Derbyshire (94) but it is difficult to assess the significance of this finding as activity was not present in most samples examined. Roche and Michitzky (18) after reviewing the evidence that goitrogens are of importance in the production of simple endemic goitre concluded that in the immense majority of cases known goitrogens are not primarily implicated in endemic goitre production. It is likely that the same can be said of simple sporadic goitre. It also seems probable that certain drugs and chemicals including iodine itself which cause goitre by interfering with thyroid hormone synthesis (95 - 102) are unlikely to be of much importance in the aetiology of sporadic simple goitre.

The element calcium has long been thought to be goitrogenic in man (103) but experimental proof of this has been/

been derived mainly from laboratory studies on the rat (104 - 6) and it is surprising that until recently (107) no isotopic studies had been made in man. The importance of calcium in the formation of simple goitre however has not yet been finally established. It may perhaps act as a goitrogen in the presence of mild iodine deficiency (104).

HEREDITY

Although heredity may be a factor in the production of simple goitre the evidence is not clear cut. Webb (108) in a study of subjects living in the goitre area of Derbyshire stated that thyroid gland enlargement was common when there had been intermarriage of relatives. Brain (109) studied the problem and came to the conclusion, on not very good evidence, that a hereditarily acquired predisposition to develop simple goitre might exist and be enhanced by environmental iodine deficiency. The acquired defect might be difficultyin the utilisation of iodine. Davenport (110) concluded that two genetic factors were involved in the inheritance of simple goitre, "one sex-linked and dominant; the other dominant but autosomal and not sex-linked". He felt that a combination of the genes in the two chromosomes was necessary for the development of goitre. Bartels (111) felt that the genetic mechanism of inherited susceptibility was of "simple monomeric recessivity with pronounced sex-limitation to women".

In 1917 McCarrison (112) was able to describe a high incidence of simple endemic goitre in a closely inbreeding tribe in the Himalayas and he believed that intermarriage accentuated the susceptibility to goitre formation.

There/

There is little doubt that the enzyme defects which cause goitres of the dyshormonogenetic type, often but not always associated with cretinism or hypothyroidism, are genetically transmitted (113 - 117). The question is, how often are genetically determined unrecognised defects in thyroid hormone synthesis responsible for the development of simple goitre or how often do minor degrees of dyshormonogenesis occur in patients with simple goitre? Abnormal ratios of monoiodotyrosines to di-iodotyrosines and of iodotyrosines to iodothyronines have been observed in patients with simple goitre (118 - 119) and many workers have noted the occurrence of abnormal iodinated proteins in the plasma and thyroids of patients who have simple goitre (85,120 - 121). These findings however are not consistently observed and it must at the moment be concluded that the significance of the well documented inherited defects in thyroid hormone biosynthesis in relation to the problem of simple goitre remains uncertain.

INFECTION

Both McCarrison (112) and Greenwald (52) have been strong supporters of the theory that simple goitre may be infectious in nature. There is little evidence that this is so but as Spence (122) has remarked, the opinions of a man like McCarrison who had spent a good deal of his life on goitre research should be treated with respect and it may be that the infectious theory of the aetiology of simple goitre deserves further study.

SUMMARY

This section reviews some of our knowledge about the aetiology of simple goitre and comes to the following conclusions.

1. Iodine deficiency, either alone, or perhaps more commonly in association with other factors can produce goitre in man.
2. There are other factors which may provoke goitre.
3. Although some of these factors such as dietary ingestion of goitrogens are known, others remain to be discovered.

REFERENCES

1. Juvenal,
Satire XIII, Line 162.

2. Popovitch, P.P. (1959),
Probl. Endokr. Gormonoter, 5, 105.

3. Jantsch, M.
Der Kropf and Seine Behandlung. Eine Geschichtliche Uebersicht, Franse Deuticke, Wien (1948) p.20.

4. Bornhauser, S.
Zur Geschichte der Schilddrusen - und Kropfforschung im 19. Jahrhundert (unter besonderer Berucksichtigung der Schweiz).
Verlag. Hr Sauerlander & Co. Aarau 1951, p.7.

5. Foote, M.N. (1954),
J. clin. Endocr. 14, 1385.

6. The Ebers Papyrus,
C.P. Bryan, London, 1930.

7. Deines, H. Von, Grapow, H. and Westendorf, W.,
Grundriss Der Medizin Der Alten Agypter IV I
Uebersetzung Der Medizinischen Texte Akademie-Verlag, Berlin (1958), p.223.

8. Mettler, C.C.
History of Medicine, The Blaikston Company, Toronto, 1947, p.813.

9. Wilson, G.M. in The Thyroid and its Diseases Ed. A.S. Mason Lippincott, Pitman, London (1963) p.

10. Hubble, D. (1964),
Practitioner 192, 321.

11. Kelly, F.C. and Snedden, W.W. in Endemic Goitre, WHO Palais des Nations, Geneva (1960) p27 ff.

12. De Smet, M.P. in Endemic Goitre. WHO Palais des Nations, Geneva (1960), p.320.

13. WHO Chronicle (1960) 14,9.

14. Chilean Iodine Educational Bureau (1946),
World Goitre Survey, London.

15./

15. Greenwald, I. (1945),
Bull. Hist. Med. 17, 229.

16. Greenwald, I. in Clinical Endocrinology I,
Ed. A.B. Astwood, Grune-Stratton Inc. New York,
U.S.A. (1960), p.123.

17. McCarrison, R. (1933),
Proc. Int. Conf. on Goitre.
Hans Huber, Berne, p.1.

18. Roche, J. and Idesitsky, S. in
Endemic Goitre, WHO, Palais des Nations, Geneva
(1960) p.351 ff.

19. Marine, D. (1922),
Physiol. Rev. 2, 251.

20. Tala, P. (1952),
Acta Endocr. (Copenhagen) Suppl. 9.

21. Taylor, S. (1953),
J. clin. Endocr. 13, 1232.

22. Trotter, W.R. (1962),
Diseases of the Thyroid Gland, Blackwell, London, p.95.

23. Chatin, A. (1850),
C.R. Acad. Sci. (Paris), 31, 280.

24. Langer, P. in
Endemic Goitre. WHO, Palais des Nations, Geneva,
(1960), p.22.

25. von Fellenberg, T. (1933),
Mitt. Lebensmitt. Hyg. 24, 123.

26. McClendon, J.F. and Williams, A. (1923),
J. Amer. Med. Ass. 80, 600.

27. De Quervain, F. (1922),
Schweiz med. Wschr. 52, 857.

28. Matovinovic, J. and Ramalingaswami, V. in
Endemic Goitre WHO, Palais des Nations, Geneva,
(1960) p.387.

29./

29. Marine, D. and Kimball, O.P. (1920),
Arch. int. Med. 25, 661.

30. Marine, D. and Kimball, O.P. (1921),
J. Amer. med. Ass. 77, 1068.

31. Marine, D. and Kimball, O.P. (1922),
Amer. J. med. Sci. 163, 634.

32. Kimball, O.P. (1937),
J. Amer. med. Ass. 108, 860.

33. Brush, B.E. and Altland, J.K. (1952),
J. clin. Endocr. 12, 1380.

34. Praverani, L. (1940),
Endokrinologie, 23, 1.

35. Wespi, H.J. (1942),
Ergebn. inn. Med. Kinderheilk. 61, 489.

36. Hood, J.L. (1953),
Bull. Wld. Hlth. Org. 9. 259.

37. Uehlinger, E.A. (1958),
Fed. Proc. 17, Suppl. 2. p.66.

38. Kimball, O.P. (1953),
Bull. Wld. Hlth. Org. 9, 241.

39. Scrimshaw, N.S., Cabezas, A., Castillo, F. and
Mendez, J. (1953),
Lancet, 2, 166.

40. Stanbury, J.B., Brownell, G.L., Riggs, D.A.,
Perinetti, H., Itoiz, J. and del Castillo, E.B.,
Endemic Goitre. The Adaptation of man to iodine
deficiency.
Harvard University Press, Cambridge, Mass. (1954).

41. Elmer, A.W.
Iodine metabolism and thyroid function. Oxford
University Press, London (1938).

42. Lamberg, B. - A., Wahlberg, P., Wegelius, O., Hellstrom, G.
and Forsius, P.I. (1958),
J. clin. Endocr. 18, 991.

43./

43. Roche, M., De Venanzi, F., Vera, J., Coll, E., Spinetti - Berti, M., Mendez - Martini, J., Gerardi, A. and Forero, J. (1957). J. clin. Endocr. 17. 99.

44. Terpstra, J. (1956), De schildklierfunctie bij endemische krop, Leiden (Theses).

45. De Visscher, M., Beckers, C., Van Den Schrieck, H - G., De Smet. M. Ermans, A.M., Galperin, M. and Bastenie, P.A., (1961). J. clin. Endocr. 21, 175.

46. Remington, R.E. (1932), J. biol. Chem. 97, ci.

47. Axelrad, A.A., Leblond, C.P. and Isler, H. (1955), Endocrinology, 56, 387.

48. Zondek, H., (1935), Diseases of the Endocrine glands. 3rd Edition. Wood. Baltimore.

49. Greenwald, I. (1955), Am. J. clin. Nutrition, 3, 215.

50. Dimitriadou, A., Ekpechi, O.L., Gadhok, R. and Fraser, T.R. (1966), Biochem. J. 99 No.1 16 p

51. Salter, W.T. (1940), The Endocrine function of iodine. Harvard University Press. Cambridge, Mass. p.12.

52. Greenwald, I. (1946), J. clin. Endocr. 6, 708.

53. Malamos, B., Miras, K., Kostamis, P., Mantos, J., Kralios, A.C., Rigopoulos, G., Zerefos, N. and Koutras, A.C., (1965). Current Topics in Thyroid Research. Ed. C. Cassano and M Andreoli, Academic Press. New York, p

54. Roche, M. (1959), J. clin. Endocr. 19, 1440.

55. Beckers, C., Barzellato, J., Stevenson, C., Gianetti, A., Pardo, A., Bobadilla, P. and De Visscher, M. (1965). Current Topics in Thyroid Research, Ed. C. Cassano and M. Andreoli, Academic Press, New York, p.838.

56./

56. London, W.T., Koutras, D.A., Pressman, A. and Vought, R.L. (1965).
J. clin. Endocr. 25, 1091.

57. Vought, R.L., Maisterrena, J.A., Tovar, E. and London, W.T. (1965).
J. clin. Endocr. 25, 551.

58. Koutras, D.A., Alexander, W.D., Buchanan, W.W., Crooks, J. and Wayne, E.J. (1960).
Lancet, 2, 784.

59. Alexander, W.D., Koutras, D.A., Crooks, J., Buchanan, W.W., MacDonald, E.M., Richmond, M.H. and Wayne, E.J. (1962),
Quart. J. Med. 31, 281.

60. Wayne, E.J., Koutras, D.A. and Alexander, W.D.
Clinical aspects of iodine metabolism, Blackwell, Oxford, (1964), p.105 ff.

61. de Crombrugghe, B., Beckers, C. and de Visscher, M. (1963)
Acta Endocr. (Copenhagen), 42, 300.

62. Boyle, J.A., Sloss, A., MacDonald, E.M. and Gray, M. (1965),
J. clin. Endocr. 25, 1035.

63. Aboul-Khair, S.A. and Crooks, J. (1965),
Acta Endocr. (Copenhagen), 48, 14.

64. De Groot, L.J. (1966),
J. clin. Endocr. 26, 149.

65. Broadhead, G.D., Pearson, I.B. and Wilson, G.M. (1965),
Brit. med. J. 1, 343.

66. Burrows, B.A. and Ross, J.F. (1953),
J. clin. Endocr. 13, 1358.

67. Rall, J.E. (1950),
J. clin. Endocr. 10. 996.

68. Cassano, C. Baschieri, L. and Andreani, D. (1957),
Rass. Fisiopat. clin. ter. 29, 253.

69. Cassano, C., Baschieri, L. and Andreani, D. (1959),
V^{e} Reunion des Endocrinologistes de langue Francaise,
p. 85.

70./

70. Cassano, C., Baschieri, L. and Andreani, D. in Advances in Thyroid Research. Ed. R. Pitt-Rivers and J.R. Tata, Pergamon Press, New York, (1961), p307.

71. Aboul-Khair, S.A., Crooks, J., Turnbull, A.C. and Hytten, F.E. (9964). Clin. Sci., 24, 195.

72. Harden, R. McG. (1963), Clin. Sci. 25, 79.

73. Harrison, M.T., Harden, R. McG., Alexander, W.D. and Wayne, E.J. (1965), J. clin. Endocr. 25, 1077.

74. Chesney, A.M., Clawson, T.A. and Webster, B. (1928), Bull. Johns Hopk. Hosp., 43, 261.

75. Marine, D., Baumann, E.J. and Cipra, A. (1929), Proc. Soc. exp. Biol. (NY), 26, 822.

76. McCarrison, R. (1931), Indian J. med. Res. 18, 1311.

77. Marine, D., Baumann, E.J., Spence, A.W. and Cipra, A. (1930), Proc. Soc. exp. Biol. (NY), 29, 772.

78. Kennedy, T.H. and Purves, H.D. (1941), Brit. J. exp. Path. 22, 241.

79. McCarrison, R. (1933), Indian J. med. Res. 20, 957.

80. Astwood, E.B., Greer, M.A. and Ettlinger, M.G. (1949), J. biol. Chem. 181, 121.

81. Altamura, M.R., Long, L. Jr., and Hasselstrom, T. (1959), J. biol. Chem. 234, 1847.

82. Astwood, E.B. (1949), Ann.int. Med. 30, 1087.

83. Greer, M.A. and Astwood, E.B. (1948), Endocrinology, 43, 105.

84./

84. Fisher, C., Epstein, D. and Paschkis, K.E. (1952),
J. clin. Endocr. 12, 1100.

85. Bastenie, P. (1947),
Lancet, 1, 789.

86. Greenwald, I. (1954),
Trans. Amer. Goiter Ass. 358.

87. Clements, F.W. (1954),
Med. J. Aust. 2, 894.

88. Clements, F.W. (1958),
Bull. Wld. Hlth. Org. 18, 175.

89. Clements, F.W. and Wishart, J.W. (1956),
Metabolism, 5, 623.

90. Gibson, H.B., Howeler, J.F. and Clements, F.W. (1960),
Med. J. Aust. 1, 875.

91. Wright, E. (1958),
Nature (Lond.), 181, 1602.

92. Peltola, P. and Vartiainen, A. (1954),
Ann. Med. Int. Fenniae, 43, 209.

93. Peltola, P. (1965),
Current Topics in Thyroid Research,
Ed. C. Cassano and M. Andreoli, Academic Press, New York,
p. 872.

94. Kilpatrick, R., Broadhead, G.D., Edmonds, C.J., Munro, D.S.
and Wilson, G.M. (1963),
Brit. med. J. 1, 29.

95. Astwood, E.B., (1943),
J. Pharmacol. Exp. Ther. 78, 79.

96. Rosenburg, I.N. (1952),
Science, 116, 503.

97. Konrower, G.M. (1951),
Brit. med. J. 2, 1103.

98. Morgans, M.E. and Trotter, W.R. (1955),
Lancet, 2, 164.

99./

99. Vanderlaan, W.P. and Bissell, A. (1946),
Endocrinology, 39, 157.

100. Wyngaarden, J.R., Wright, B.M. and Ways, P., (1952),
Endocrinology, 50, 537.

101. Morton, M.E., Chaikoff, I.L. and Rosenfeld, S. (1944),
J. biol. Chem. 154, 381.

102. Begg, T.B. and Hall, R. (1963),
Quart. J. Med. NS. 32, 351.

103. Murray, M.M., Ryle, J.A., Simpson, B.W. and Wilson, D.C. (1948),
M.R.C. Memoir, No. 18, London, p.26.

104. Hellwig, C.A. (1934),
Endocrinology, 18, 197.

105. Thomson, J. (1933),
Arch. Path. (Chicago), 16, 211.

106. Taylor, S. (1954),
J. clin. Endocr. 14, 1412.

107. Boyle, J.A., Greig, W.R., Fulton, S. and Dalakos, T.G. (1966),
J. Endocr. 34, 111.

108. Webb, W. (1886),
Brit. med. J. 1, 686.

109. Brain, W.R. (1927),
Quart. J. Med. 20, 303.

110. Davenport, C.B. (1932),
The genetical factor in endemic Goitre.
Publication 428, Carnegie Institute of Washington.

111. Bartels, E.D. (1941), Heredity in Graves Disease with remarks on Heredity in Toxic Adenoma in the Thyroid, non-toxic goitre and myxodema. Thesis, Copenhagen.

112. McCarrison, R.
The Thyroid Gland in Health and Disease.
Balliere, Tindall and Cox, London, 1917. p.58

113./

113. Lelong, M., Joseph, R., Canlorbe, P., Job, J. - C., Plainfosse, B. (1956), Arch. franc. Pediat. 13, 1.

114. Stanbury, J.B. and McGirr, E.M. (1957), Amer. J. Med. 22, 712.

115. Hutchison, J.H. in Recent Advances in Paediatrics, 2nd Ed. Ed. D. Gairdner, J. and A. Churchill, Ltd., London, 1958, p.172.

116. Hutchison, J.H. and McGirr, E.M. (1956), Lancet, 1, 1035.

117. Stanbury, J.B., Meijer, J.W.A. and Kassenaar, A.A.H. (1956), J. clin. Endocr. 15, 54.

118. Pitt-Rivers, R., Hubble, D. and Heather, W.H. (1957), J. clin. Endocr. 17, 1313.

119. Dimitriadou, A., Fraser, Slater, J.D.H. and Wagner, H., Advances in Thyroid Research. Ed. R. Pitt-Rivers, Pergamon Press, Oxford, 1961. p.313

120. Dowling, J.T., Ingbar, S.H. and Freinkel, M. (1961), J. clin. Endocr. 21, 1390.

121. Kahn, A., Cogan, S.R. and Berger, S. (1962), J. clin. Endocr. 22, 1.

122. Spence, A.W. (1952), Brit. med. J. 2, 529.

PART 1

SECTION 2

THE VALIDATION OF THE IODINE:CREATININE RATIO TECHNIQUE OF PLASMA INORGANIC IODINE MEASUREMENT

This part of this section of the thesis is concerned principally with a validation of the method I used to measure plasma inorganic iodine (PII) in the twins. Methods in use at present involve measurement of PII by indirect means (1,2), the most usual of these methods being some form of isotope dilution technique (1,3 - 9). Isotope dilution methods however are time consuming and require the administration of radioactive materials. For these reasons I thought that they were not suitable for PII measurement in the healthy, mainly young twins I was intending to study.

I decided to explore the usefulness of a method of PII measurement described by Vought et al (10) which involves comparison of the iodine and creatinine ratios in blood and urine (I/Cr ratio method) and which requires from the subject no more than a casual sample of urine and a venesection. It seemed likely that this might be a valuable technique with which to measure PII levels in the twins. Vought et al commented that it remained to be shown that the I/Cr ratio method of PII measurement gave reliable results in patients on a normal diet under conditions of normal activity nor did they compare the results of the method with the results of the isotope dilution method.

Accordingly/

Accordingly I undertook a comparison of the PII values obtained by an isotope dilution technique with these obtained using the I/Cr ratio method in hospital outpatients. I studied euthyroid patients, patients who had simple goitre with a 24 hour thyroidal ^{131}I uptake > 40 per cent and patients with thyrotoxicosis.

Vought et al (5) utilised a method based on the knowledge that iodine is filtered at the glomerulus and that approximately 75% of the iodine in the filtrate is reabsorbed by the renal tubule. Accordingly, urinary inorganic iodine accounts for approximately 25% of the total load filtered.

Thus:

$$\text{Glomerular filtration rate (GFR) (l)} \times \text{PII (ug/l)} = \text{Urine iodine (ug/l)} \times 4 \times \text{Urine volume (l/day)} \quad (1)$$

They measured GFR as the renal clearance of creatinine.

Thus:

$$\frac{\text{PII (ug/l)} \times \text{Urine creatinine (ug/l)} \times \text{Urine volume}}{\text{Serum creatinine}} = \text{Urine iodine (ug/l)} \times 4 \times \text{Urine volume (l/day)} \quad (2)$$

or/

or

$$\text{PII (ug/100 ml)} = \frac{\text{Urinary iodine (ug/100 ml)} \times 4 \times \text{Serum creatinine (mg/100 ml)}}{\text{Urine creatinine (mg/100 ml)}} \quad (3)$$

The isotope dilution technique depends on a comparison of the specific activities of radioiodine in blood and urine at a given time.

Thus

$$\frac{\text{PII (ug/100 ml)}}{\text{Plasma radioiodine (cps/100 ml)}} = \frac{\text{Urinary iodine (ug/100 ml)}}{\text{Urinary radioiodine (cps/100 ml)}} \quad (4)$$

i.e., PII (ug/100 ml)

$$= \frac{\text{Urinary iodine (ug/100 ml)}}{\text{Urinary radioiodine (cpm/100 ml)}} \times \text{Plasma radioiodine (cps/100 ml)} \quad (5)$$

This/

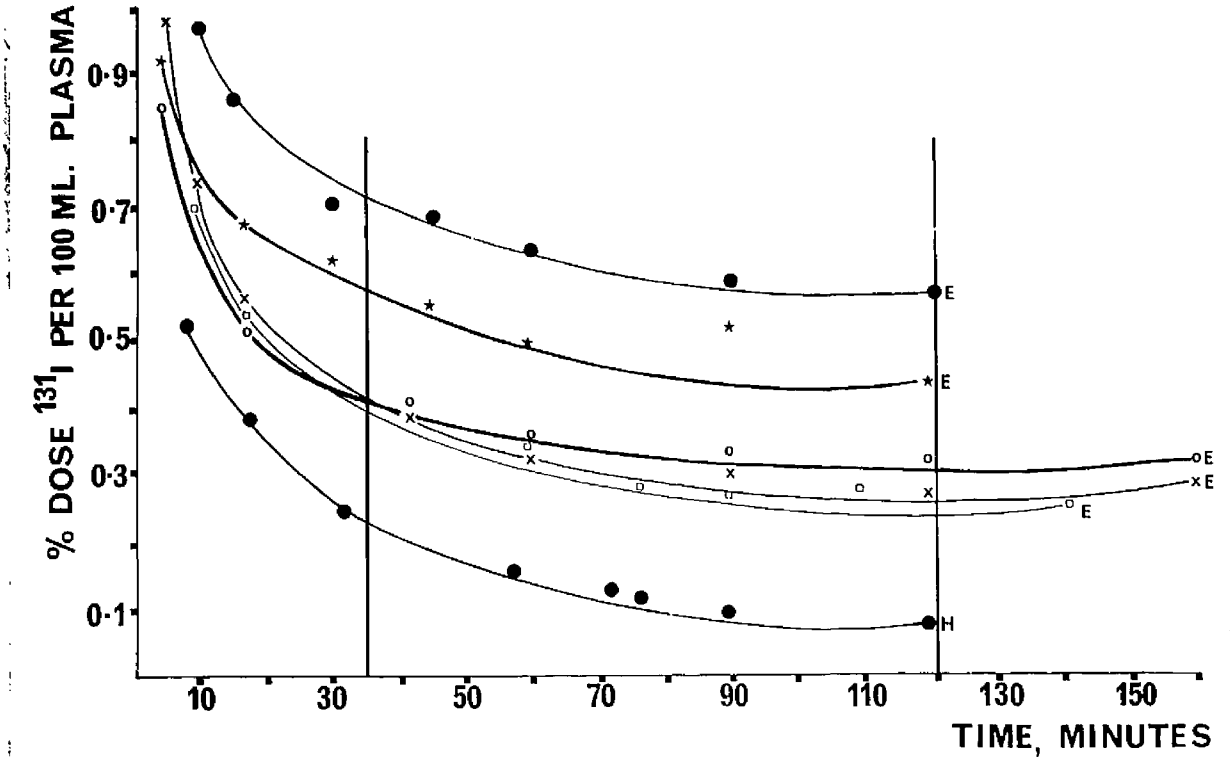

FIGURE 1 Plasma radioiodine levels following intravenous injection of ^{131}I. E = euthyroid patient, H = hypothyroid patient. Curves have been fitted by eye to the data from the 6 patients in order to avoid confusion as to which point derives from which patient. The average plasma radioactivity from 35 to 120 min. was calculated from these data for each patient.

This method is discussed fully by Stanley (1) and an excellent account has been given more recently by Alexander, Koutras, Crooks, Buchanan, Macdonald, Richmond and Wayne (11).

Initial Experiment

Initial experiments in 6 patients showed that, after the intravenous injection of radioiodine, the plasma level of radioactivity falls slowly with time from 35 to 120 min from the time of injection (Fig. 1), and a midpoint blood sample taken 77 min after radioiodine injection gives the average plasma radioactivity. To show that this was so, it was necessary to compare the midpoint blood sample at 77 min with the average plasma radioactivity between 35 and 120 min. To obtain this average plasma radioactivity it was necessary to find an equation which would represent the fall of plasma radioactivity with time; integration of this equation gave the average plasma radioactivity over the time of study. As facilities were available, a computer was used to find the equations best fitting the data on disappearance of plasma radioactivity in the 6 patients studied. Equations which fitted the data reasonably were found with cubic and parabolic functions. The curves representing these functions are shown fitted to the data from 1 patient in Fig. 2, and it is evident that there is a reasonable fit. Integration was carried/

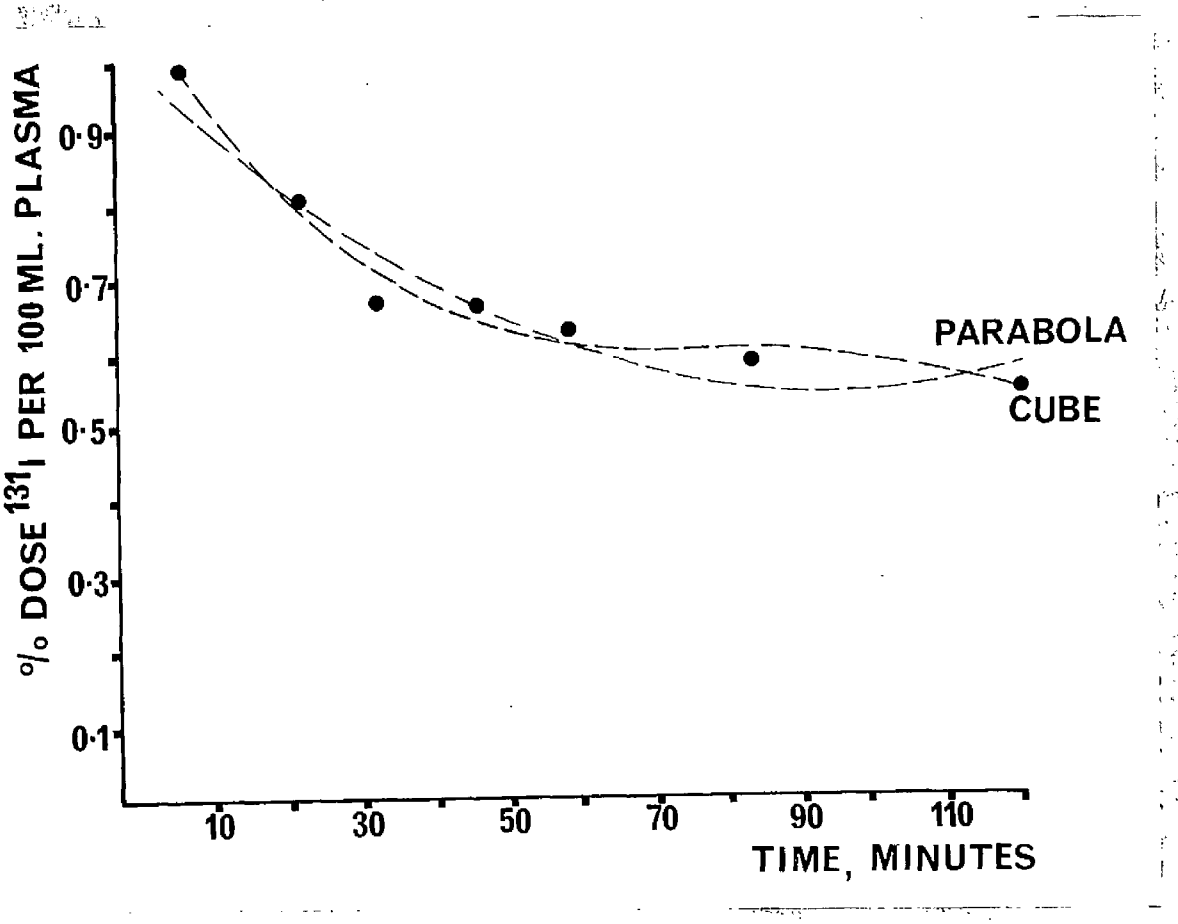

FIGURE 2 The line which best fits the points representing the fall of plasma radioactivity with time following intravenous injection of ^{131}I lies between a parabolic and a cubic function.

carried out using both functions. The average of the 2 integrations between 35 and 120 min was taken as representing the average plasma radioactivity.

It is appreciated that a polynomial function does not theoretically fit the disappearance curve of plasma radioiodine as this is multiexponential (12,13). In practice, however, multiexponential curves are difficult to fit to data and accordingly polynomial functions were chosen for curve fitting as they do give an accurate representation of the curve of plasma ^{131}I disappearance from zero to 120 min. By integrating the polynomial functions chosen, a valid result for average plasma radioiodine levels over the period of study is obtained.

The actual plasma radioactivity at 77 min was found by substituting 77 for X in both functions, and again an average of the 2 values obtained was taken. Table 1 (p. 239) shows the values obtained by integration (the average plasma radioactivity from 35 to 120 min) compared with the values obtained by substitution (the plasma radioactivity at 77 min). There is a good agreement between the values obtained by each method. (Correlation coefficient = 0.99 difference between means of observations not significant $t = 0.31$ $0.8 > P < 0.7$).

It is valid to relate plasma specific activity to urine specific activity according to equation (5) over the period/

period 35 - 120 min following intravenous injection of radioiodine.

Materials

Fifty six hospital out-patientswho had received no special instructions about their diet were studied in the non-fasting state. Thirty one patients were euthyroid on clinical grounds and on the results of PB^{127}I estimations and routine ^{131}I studies. Sixteen patients had a simple goitre and a 24 hour thyroidal ^{131}I uptake > 40 per cent. These patients were therefore similar to the group described by Wayne et al. in Glasgow (11,14) who had a 48 hour ^{131}I uptake > 40 per cent. Nine patients had untreated thyrotoxicosis.

Methods

Thirty five min after the intravenous administration of approximately 25 uc of radioiodine, the bladder was completely emptied and the urine was discarded (33 patients received ^{131}I and 23 received ^{132}I). Each patient then drank a large glass of water to ensure that it would be possible to void urine at 120 min. The 120-min specimen was collected in specially prepared ^{127}I-free glassware for estimation of radioactivity, ^{127}I and creatinine. A 5 ml blood sample was taken into a heparinised bottle,

77/

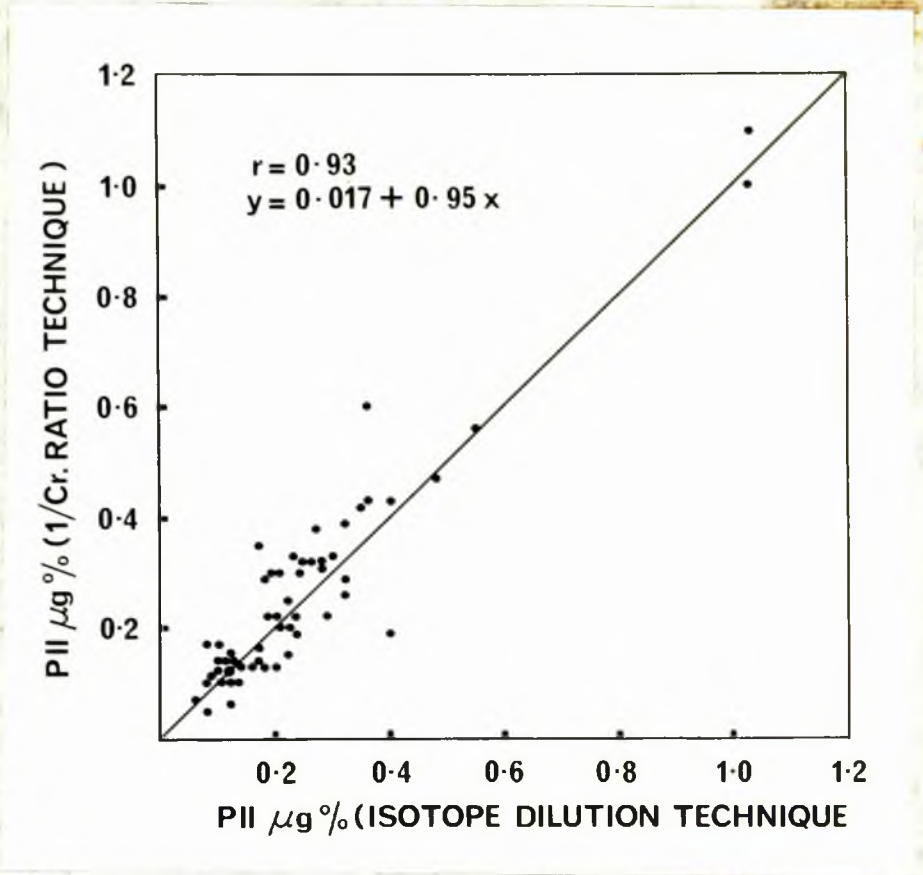

FIGURE 3 Shown are the PII values given by an isotope dilution technique plotted against the PII values given by the I/Cr ratio technique in the same subject at the same time.

77 min after the radioiodine injection for estimation of radioactivity and creatinine.

One ml samples of urine and plasma were assayed for radioactivity in a well-type scintillation counter (Nuclear Enterprises (G.B.) Ltd.), using a thallium-activated sodium iodide crystal.

Plasma and urine creatinine were measured by the alkaline picric acid method (15). Urine ^{127}I was estimated by the method of Farrell and Richmond (16); analyses of ^{127}I were performed in duplicate on each sample.

The PII value was calculated from equations (3) and (5).

Results

The results are shown in Table 2(p. 241) and individual values obtained by each method for individual subjects are shown in Appendix A (p.245). Fig. 3 shows that when PII determinations by both methods were compared in the same plasma and urine samples there was a very close agreement obtained between each method. Because one factor is common to both methods (urinary ^{127}I estimation) it was necessary to correlate with each other only the independent variables used in the calculation of PII by each/

each method (namely the ratio $\frac{\text{plasma creatinine}}{\text{urine creatinine}}$ with the ratio $\frac{\text{plasma radioiodine}}{\text{urine radioiodine}}$.) If one studies the reciprocal of these ratios multiplied by urine volume in a given unit of time a measure of the renal clearances of iodide and creatinine results.

(this follows from the relationship:

$$\text{renal clearance} = \frac{\text{urine concentration}}{\text{plasma concentration}} \times \text{Volume in unit time})$$

I found a highly significant correlation coefficient ($r = 0.90$) for this plot (not shown) and the slope of the regression line when drawn through the origin was 3.61. This meant that the $\frac{\text{Plasma radioiodine}}{\text{urine radioiodine}}$ ratio was on average 3.61 times greater than the ratio $\frac{\text{plasma creatinine}}{\text{urine creatinine}}$. Therefore in calculating PII from equation (3) I used the factor 3.6 rather than the factor 4 as described by Vought and his colleagues (10). Using this factor the correlation coefficient for the two methods was 0.93 and the regression equation calculated from the formula (7)

$$y = a + b\,(x - \bar{x})$$

where $a = \bar{y}$

and $b = \dfrac{\Sigma(y - \bar{y})\,(x - \bar{x})}{\Sigma(x - \bar{x})^2}$

was $y = 0.017 + 0.95\,x$ (Fig. 3)

Theoretically/

Theoretically the regression line should cut zero whereas it cuts the y ordinate at 0.017. This is not however significantly different from zero.

When the patients were studied in groups, as euthyroid, hyperthyroid or simple goitre a good correlation obtained within the group (Table 2p.241) and there was no statistically significant difference seen between the results given by each method in any group.

Discussion

The PII values obtained by either method have the same precision and are in the same range as those reported by other workers some of whose findings are shown in Table 3(p.243). In addition, Berson and Yalow (18) measuring hormonal iodine utilisation rates and thyroid iodine clearance rates, indirectly estimated the PII in four euthyroid subjects to be 0.43 ug per cent (range 0.22 - 0.87) while Riggs (19) has calculated a value of 0.30 ug per cent. The differences in results from various centres are probably accounted for as much by variation in dietary intakes of iodine in different geographical areas as by small differences in technique.

In an early study reported from Glasgow, where the present/

present study was made, Wayne's group reported a mean PII value of 0.30 ug per cent (20). Later (11) these workers reported the mean PII value in 33 control subjects to be 0.19 ug per cent which is much lower than the values I obtained. I used an intravenous isotope dilution method whereas Wayne's group used an oral isotope dilution technique. I do not feel however that this slight methodological variation accounts for the observed differences which may rather be due to 2 factors. Firstly, I have included 2 patients who had obviously ingested excess dietary iodine recently as their PII values were $\geq$ 1.00 ug per cent. Secondly, and perhaps more importantly, my subjects were in the non-fasting state whereas the group studied by Wayne et al (11) were fasting. These authors comment that the PII level is likely to be higher in the non-fasting state (11). I feel that if one believes that simple goitre is due to or in any way associated with dietary deficiency of iodine one should study individuals in the non-fasting state as very high PII levels due to recent iodine ingestion should be found significantly less often in the group with simple goitre.

The I/Cr ratio technique of PII measurement is a reliable one because a high degree of correlation exists between/

between results given by it compared with the results given by an isotope dilution method. This suggests that the factor 3.6 which I substituted for the factor 4 in equation (3) was the correct one to use. Indirect confirmation of the correctness of this factor can be gained if one attempts to calculate tubular reabsorption of iodide using it and then compares the result with the experimental observations of others. Accepting creatinine clearance as a rough measure of GFR then

3.6 x urinary iodide

= iodide filtered at glomerulus. (6)

Let iodide filtered at glomerulus

= 100 per cent (7)

then urinary iodide

$$= \frac{100 \text{ per cent of iodide filtered at glomerulus}}{3.6}$$

= 28.8 per cent (8)

Thus tubular reabsorption of iodide = 100 - 28.8 per cent

= 71.2 per cent

This calculated figure agrees with the measurements of Perry and Hughes (3) who reported a figure of 72.9 per cent and of Bricker and Hlad (21) who found a value of 73.2 per cent for tubular reabsorption of iodide. Moreover London and his colleagues/

colleagues (22) later published findings very similar to my own. They found that the factor 3.64 fitted equation (3) and calculated tubular reabsorption of iodide on this basis to be 72.6 per cent.

The I/Cr ratio technique of PII measurement has some obvious limitations. As it depends on the integrity of the kidneys in respect of its iodide filtering and iodide reabsorbing capacities, it seems unlikely that the method would be applicable to PII measurement in renal failure. Perry and Hughes (3) observed an increase in tubular reabsorption of iodide in severe renal disease and Alexander et al (25) noted that during the total fasting of obese patients, a marked decrease in the renal clearance of iodide occurred. This decrease was not paralleled by a decrease in the creatinine clearance. As I was intending to use the method for PII measurement in healthy subjects derived from the general population, it did not seem probable that these limitations would invalidate my use of the procedure.

This preliminary study confirmed the findings of Wayne et al (14) that the PII was low in patients who attend Hospital with simple goitre and who have a ^{131}I uptake > 40 per cent (Table 2 p.241). I did not find quite the striking separation reported by these authors between PII/

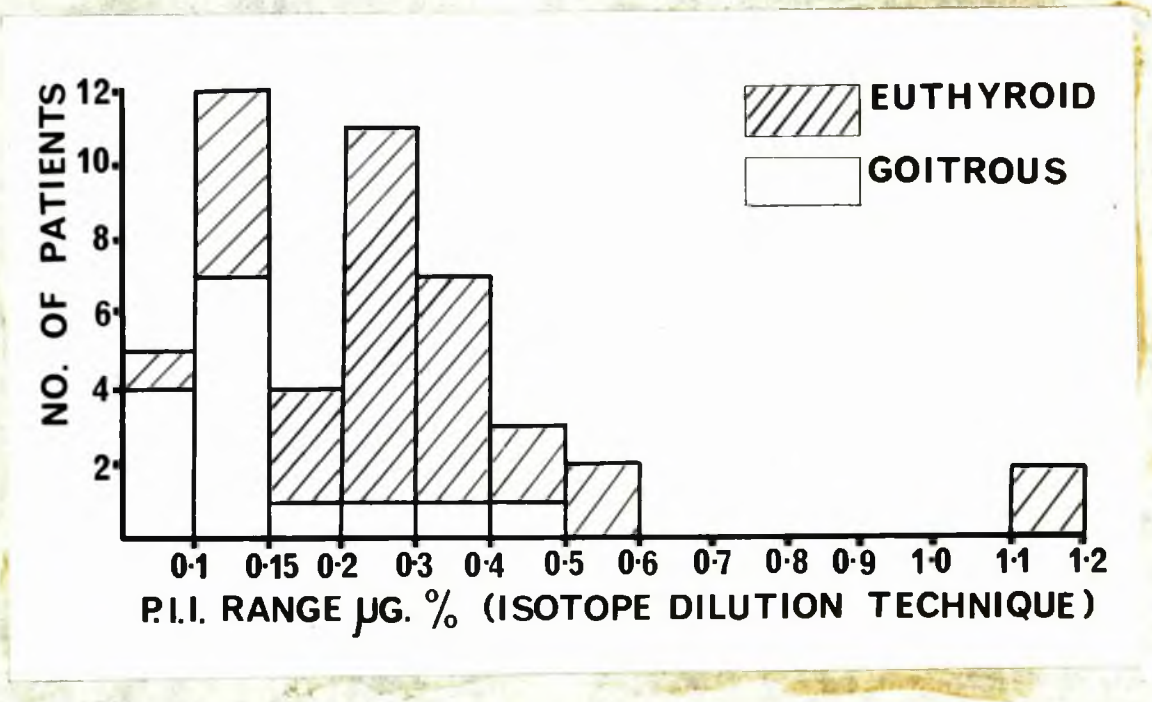

FIGURE 4 PII values in 31 euthyroid subjects and 16 patients with simple goitre whose 24 hour thyroidal ^{131}I uptake was 40 per cent. Four goitrous patients have PII values > 0.15 ug per cent. PII levels in 6 euthyroid non-goitrous subjects were < 0.15 ug per cent. (AII values by isotope dilution technique)

PII values in patients with simple goitres compared with normal controls. As can be seen in Fig. 4, 4 of the patients with simple goitre had PII values ≥ 0.15 ug per cent and 6 out of 31 euthyroid patients had PII values < 0.15 ug per cent.

The next section of this part of the thesis will describe the use to which I put the I/Cr ratio method in an effort to explore further the relationship between PII levels and simple goitre in Glasgow and the West of Scotland.

SUMMARY

This section deals with a validation of the iodine-creatinine urine-plasma (I/Cr ratio) technique of plasma inorganic iodine (PII) estimation (10). This method was used to measure PII values in the study described in the next section of the thesis. The results given by the I/Cr ratio technique were compared with those given by an isotope dilution method. An initial experiment describes an attempt to validate the assumption that after intravenous administration of radioiodine, in the isotope dilution method, a blood sample taken at the middle of a certain period gives an accurate estimation of the average plasma radioactivity over that period. This assumption was verified by a computer analysis of experimental data obtained in 6 subjects where curves were fitted to the observed fall of plasma radioactivity with time after intravenous injection of radioiodine. Average plasma radioactivity values were obtained for the period 35 to 120 minutes following isotope administration by integration of these curves. These values were compared to those given by substitution of the midpoint value for time (77 min.) in the equations and a good correlation was found between them.

The/

The results given by both techniques of PII measurement were found to give an acceptable correlation in 31 euthyroid subjects, 16 patients with simple goitre and 9 patients with untreated thyrotoxicosis but I found that the correlation could be made even better by changing the constant 4 in the equation used to calculate PII by the I/Cr ratio technique to the value 3.6.

An overall comparison of the results then obtained by the 2 methods gave a correlation coefficient of 0.93 and the regression of PII values by the isotope dilution technique on values by the I/Cr ratio technique was represented by the equation $y = 0.017 + 0.93 x$.

The study therefore validates the I/Cr ratio technique as a means of PII measurement. The better correlation found when the constant 3.6 was used in calculation of PII by the I/Cr ratio method suggests, on theoretical grounds, that 71 per cent of the iodide filtered at the renal glomerulus is re-absorbed by the kidney tubules and this calculated value agrees well with the experimental observations of others (3,21).

REFERENCES

1. Stanley, M.M. (1949),
J. clin. Endocr. 9,941.

2. Berson, S.A. (1956),
Amer. J. Med. 20,653.

3. Perry, W.F. and Hughes, J.S.F. (1952),
J. clin. Invest. 31,457.

4. Zingg, W. and Perry, W.F. (1953),
J. clin. Endocr. 13,712.

5. Reilly, W.A., Scott, K.G., Searle, G.L. and Castle, J.N. (1953),
Metabolism, 7,699.

6. Feinberg, W.D., Hoffman, D.L. and Owen, C.A. (1959),
J. clin. Endocr. 19,567.

7. Fitting, W. (1960),
J. clin. Endocr. 20,569.

8. Abdul-Khair, S.A., Crooks, J., Turnbull, A.C. and Hytten, F.E. (1964),
Clin. Sci. 27,195.

9. De Crombrugge, B., Beckers, C. and De Visscher, M. (1963),
Acta. Endocr. (Copenhagen), 42,300.

10. Vought, R.L., London, W.T., Lutwak, L. and Dublin, T.D. (1963),
J. clin. Endocr. 23, 1218.

11. Alexander, W.D., Koutras, D.A., Crooks, J. Buchanan, W.W., MacDonald, E.M., Richmond, M.H. and Wayne, E.J. (1962).
Quart. J. Med. NS 31,281.

12. Hays, M.T. and Wagner, L.H. (1965),
J. appl. Physiol. 20, 1319.

13. Hays, M.T. and Solomon, D.H. (1965),
J. clin. Invest. 44, 117.

14. Wayne, E.J. Koutras, D.A. and Alexander, W.D.
Clinical Aspects of Iodine Metabolism, Blackwell Scientific Publications, Oxford, 1964, p.107.

15./

15. Hare, R.D. (1950).
Proc. Soc. Exp. Biol. Med., 74, 148.

16. Farrell, L.P. and Richmond, M.H. (1961).
Clin. Chim. Acta. 6,620.

17. Dunnicliff, K.A. (1957).
Industrial Experimentation, H.M. Stationary Office,
London, 4th edition, p.62.

18. Berson, S.A. and Yalow, R.S. (1954).
J. clin. Invest. 33,1532.

19. Riggs, D.S. (1952).
Pharmacol. Rev. 4,284.

20. Koutras, D.A., Alexander, W.D., Buchanan, W.W., Crooks, J.
and Wayne, E.J. (1960).
Lancet, 2, 784.

21. Ericken, M.S. and Hlad, C.J. (1959).
J. clin. Invent., 34, 1057.

22. London, W.T., Koutras, D.A. and Vought, R.L. (1964).
J. clin. Endocr. 24, 1231.

23. Alexander, W.D., Hendon, R.McG., Koutras, D.A. and
Harrison, M.H. (1964).
Metabolism, 13,567.

PART 1

SECTION 3

THE ROLE OF HEREDITARY AND ENVIRONMENTAL FACTORS (IODINE DEFICIENCY) IN THE AETIOLOGY OF SMALL SIMPLE GOITRES IN THE GLASGOW AREA: APPLICATION OF THE TWIN STUDY METHOD

Simple goitre is thyroid enlargement which is not associated with thyrotoxicosis, or the consequence of thyroiditis neoplasm, dyshormonogenesis or goitrogen administration (1). Within the United Kingdom the prevalence of simple goitre varies geographically and it is more common in females (2-5). Although lack of iodine appears to be important in the causation of both endemic (6) and sporadic (7) simple goitre, most workers concede that there are other, as yet unidentified, aetiological factors which together with iodine deficiency either initiate or maintain the thyroid enlargement (1,3,7,8). In this respect an inherited sensitivity to a relative insufficiency of dietary iodine leading to thyroid hypertrophy has been postulated to account for simple goitres (9,10).

It has, however, been difficult to differentiate the relative importance of inheritance from that of iodine deficiency alone as a cause of goitre in individuals in communities within the United Kingdom; the population is composed of individuals and families who are both genetically heterogeneous and variable in their dietary habits.

In the present investigation some of the difficulties in differentiating genetic from environmental factors in the aetiology of simple goitre were circumvented by the application of the twin study method.

TWINS AND THE TWIN STUDY METHOD

The twin study method was first proposed as a technique for differentiating the influence of heredity from that of environment by the famous geneticist F. Galton (11) in one of his most important contributions to the science of human genetics (12). His paper "The history of twins as a criterion of the relative powers of nature and nurture" published in 1875 ushered in an epoch which was to be characterised by investigations into the relative roles of heredity and environment in the formation of character and physical attributes (12). Galton pointed out that since identical twins have exactly the same hereditary structure, differences observed between them must be caused by environment. Non-identical twins who are genetically similar but not identical can be used for purposes of comparison quite conveniently. As Penrose (12) has remarked the argument is often put the wrong way round, that is to say it is supposed that, if a pair of identical twins are alike in any given trait, this trait must be hereditary. This may be so but such an occurrence would be only a small item in the proof.

There exist obvious geographical and racial differences in the incidence of twin confinements. Among the people of/

of east Asia, multiple births are rare; for instance, in Japan the incidence is 3.6 per thousand (1:276). In Europe, there tends to appear a progressive decrease in the frequency of twins from north to south. The incidence of human twinnings in the northern countries of the Continent is one of the highest in the world, ranging from 14 to 16 per thousand (1:70 to 1:63) (13).

The majority of research workers have considered the ultimate cause of dizygotic twinning (dissimilar twinning, polyovulation, or the release of extra eggs) to be genetic in nature (14,15,16,17,18,19). The increase in incidence becomes more manifest with a rise in maternal age and/or parity (birth ranks). The rate of dizygotic twinning rises from zero at puberty to the attainment of a maximum at about 35 to 39 years of age, and then reverts abruptly to zero at the menopause. The rate of monozygotic twinning (identical twinning, polyembryonia or division of the embryo) rises but slowly, or is not dependent upon age (16,17,20).

It has also been suggested that the incidence of twins, with respect to both human beings and animals, varies according to climate, attaining a peak in cold, and falling to the lowest rate in warm localities (20). Other investigators have laid stress upon social factors (21,22,23). In towns, the frequency of multiple births is lower than that in the surrounding rural areas also when one compares the incidence/

incidence among mothers in the various age groups (20). In pregnancies with multiple zygotes, there exists increased risk of spontaneous abortion and prematurity, together with high intrauterine mortality and a high still-birth rate (15,16,22). The social standing of mothers also has its significance in the prematurity of twins, occurring more often in the lower social classes (15,22).

As Penrose (12) has commented caution must be exercised before too readily drawing inferences from the facts of similarity and dissimilarity between twin pairs, about the relative influences of environment and heredity. Fraternal twins may on rare instances develop an extraordinary similarity at an early age of development if there is an exchange of embryonic cells due to their blood circulation coming into contact through the placenta. This is the "placental transfusion" syndrome. In Genesis (24) we read of the birth of Esau and Jacob where "the first came out red"; some authors (25) believe that this may have been the first description of the placental transfusion syndrome. As it is however a rare occurrence (25) one way to circumvent difficulties it might cause in interpretation of results, is to study large numbers of twins as has been done in the present study. Identical twins may share a closer commoner environment than do non-identical twins and this fact may cause/

cause the estimate of the role of hereditary factors to be too high. The twin study method therefore is possibly more useful for demonstrating that environmental rather than hereditary factors are of importance in the development of a given trait or attribute.

Notwithstanding these considerations the twin study method has been exploited extensively in recent years in the assessment of the role of nature and nurture in a wide variety of physical attributes and disease states (26 - 40) and the technique is of established used in the investigation of problems in clinical genetics. It has not however been used before in a study of goitre. In the present study healthy twins from the West of Scotland were examined for the presence or absence of simple goitre. A comparison was made of the concordance rates for goitre (both of a twin pair having simple goitre) in the monozygotic (genetically identical) and in the dizygotic (genetically non-identical) twin pairs. If the twins are young and have not yet separated from one another, as was mainly the case in this study, they may be assumed to share a common environment. Any differences in concordance rates observed between mono- and dizygotic pairs may then be ascribed to the closer genetic constitution of the monozygotic twins compared with the dizygotic twins. The technique thus gave an index of/

of the importance of genetic factors in the aetiology of simple goitre.

Plasma inorganic iodine (PII) concentrations were also measured in most of the twins and the values were correlated with the presence or absence of simple goitre. It was therefore also possible to assess the importance of iodine deficiency, as revealed by a low PII, in the formation of the small simple goitres which were found in these young twins.

TWIN SAMPLE

One hundred and seventy four twin pairs from the west of Scotland who volunteered in response to my ascertainment campaign for twins were studied. I had notices posted in major hospitals in the city of Glasgow and an article of general interest on the value of twins in medical research written in a Glasgow evening newspaper with a circulation of 300,000 people. In addition with the co-operation of the Director of Education and Medical Officer of Health for Glasgow Schools, I wrote personally to most of the headmasters of secondary schools in and around Glasgow for the names of twin schoolchildren. I then wrote to the parents of these children asking for their co-operation in the study. No person under 12 years of age was included in the study. Details of the twin pairs are shown in Table 1 (p.250) which also shows how many of the twins had been living apart from each other for more than 1 year.

Determination of Zygosity Each of the 174 twin pairs was examined by myself. The criteria of Newman et al (41) were employed in the determination of zygosity. The twin pairs were seen together. The unlike sex pairs were obviously not identical. The like sex pairs were examined in respect of general and facial likeness, colour and texture of the skin, colour and texture of the hair, colour and structure of the iris, skin colour, and general morphology/

morphology of teeth, hands, fingers and types of nails. The following blood group antigens were determined (by Dr. R. MacAndrew, Blood Transfusion Department, Glasgow Royal Infirmary) A_1, A_2, B,O; M,N,S,s; C,D,E,c,e; Kell; Duffy and P. These antigens were then compared in each like sex twin pair. In addition I personally took finger and palm print impressions from each like sex pair and these were examined for confirmation of zygosity in respect of fingerprint patterns and ridge counts using the criteria of Holt (42). (This examination was carried out by Chief Superintendent Hamilton of the Identification Bureau, City of Glasgow Police Headquarters). It is likely that the probability of making a correct diagnosis of monozygosity in any pair of monozygotic twins on the basis of these data is well over 90 per cent (43) and it is 100 per cent for dizygotic twins because dizygosity was diagnosed in like sex pairs only when there was unequivocal evidence (such as a different iris colour, blood group or fingerprint pattern). Fifteen twin pairs thought to be monozygotic subsequently underwent reciprocal split skin grafting from each other on two consecutive occasions. Only one pair showed a graft rejection reaction. The diagnosis of monozygosity was thus correct in 93 per cent of this small series if one accepts tolerance of a skin graft from the other twin on two consecutive occasions as the ultimate criterion of monozygosity.

The Criteria of Scitre/

The Criteria of Goitre

The difficulties in defining goitre size have been fully discussed by Kilpatrick et al (4). I personally examined each of the twins for goitre and I considered it to be present only when thyroid tissue was both visible and palpable. Each subject was examined in the sitting position in a diffuse light which gave even illumination. I sat facing the subject whose neck was exposed. The subject was then asked to swallow, a glass of water being given if spontaneous swallowing was difficult and I looked for a swelling in the thyroid region. This procedure was repeated as I looked obliquely from the right and then from the left. If a swelling in the neck appeared to move upwards on swallowing it was rendered as "thyroid visible".

To palpate the gland, I stood behind each subject with my thumbs over the nape of the slightly flexed neck. My index and middle fingers were held medially to the anterior border of the sternomastoid muscle. The subject was then asked to swallow three times and any swelling felt to move on swallowing was rendered as "thyroid palpable". This criterion of goitre corresponds to the Class 2 enlargement of Kilpatrick et al (4) and is the same criterion which was used in the goitre survey of Crooks et al (44). Most of the goitres encountered were small. An example of the average goitre/

FIGURE 1 This is a representative example of the average goitre size which I found in the twin survey. This twin has been photographed in the act of swallowing with a diffuse light directed on to the neck from her left. The shadow of the thyroid is plainly visible in the midline while she is swallowing. This gland was quite easily palpable and was in reality more readily visible than the photograph suggests.

goitre size encountered is shown in Fig. 1. When I was in doubt about the presence or absence of visible and palpable thyroid enlargement the examination was independently repeated by a colleague who had at that time the same experience as myself (3 years') in thyroid gland disorders. Whenever we disagreed, goitre was considered absent. It has been shown (44) that observer error between reasonably experienced clinicians was minimal when this method was employed in a field survey of goitre.

Measurement of Plasma Inorganic Iodine This was carried out using the indirect non-isotopic iodine creatinine ratio technique which I have described fully and validated experimentally in the previous section of this part of the thesis. PII was not measured in the first 34 twin pairs seen but thereafter was estimated in every twin pair who volunteered for study until the investigation was finished. Thus PII values were assessed in 120 pairs.

Procedure

As one of the aims of the study was to investigate the role of dietary iodine deficiency in the causation of simple goitre the twins were not advised concerning diet so that they could be studied under conditions of normal diet in their usual day to day circumstances and in the non-fasting state.

The large majority were examined between 9.30 a.m. and 3.00 p.m. It has been shown both in England and in Scotland/

Scotland that there are large seasonal fluctuations in the iodine content of milk, high levels of iodine being found in winter and early spring and low levels in summer (45). The twins were studied from November to April inclusive and it is therefore unlikely that variation in the iodine content of milk over the period of study might invalidate a comparison between PII values found at the beginning of the study with those found at the end of the study.

After the procedures for the determination of zygosity had been completed, each twin was examined for the presence or absence of goitre. Venous blood was then taken for estimation of blood group antigens and serum creatinine. In addition, tests for antibody to thyroglobulin by a tanned red cell haemagglutination technique (46) and for antibody to thyroid cell "microsomal" antigen by an immunofluorescent sandwich technique (47) were also performed on this blood sample. A 20 ml. urine sample was collected in especially prepared ^{127}I free glassware immediately after venesection. Creatinine was estimated in blood and urine by the method of Hare (48) and duplicate estimations of inorganic iodine were made on each urine sample by the method of Farrell and Richmond (49). PII was calculated from the formula:

$$PII\ (\mu g\ per\ cent) = \frac{\text{serum creatinine (mg per cent)} \times \text{urine iodine (}\mu g\ per\ cent\text{)} \times 3.6}{\text{urine creatinine (mg per cent)}}$$

RESULTS/

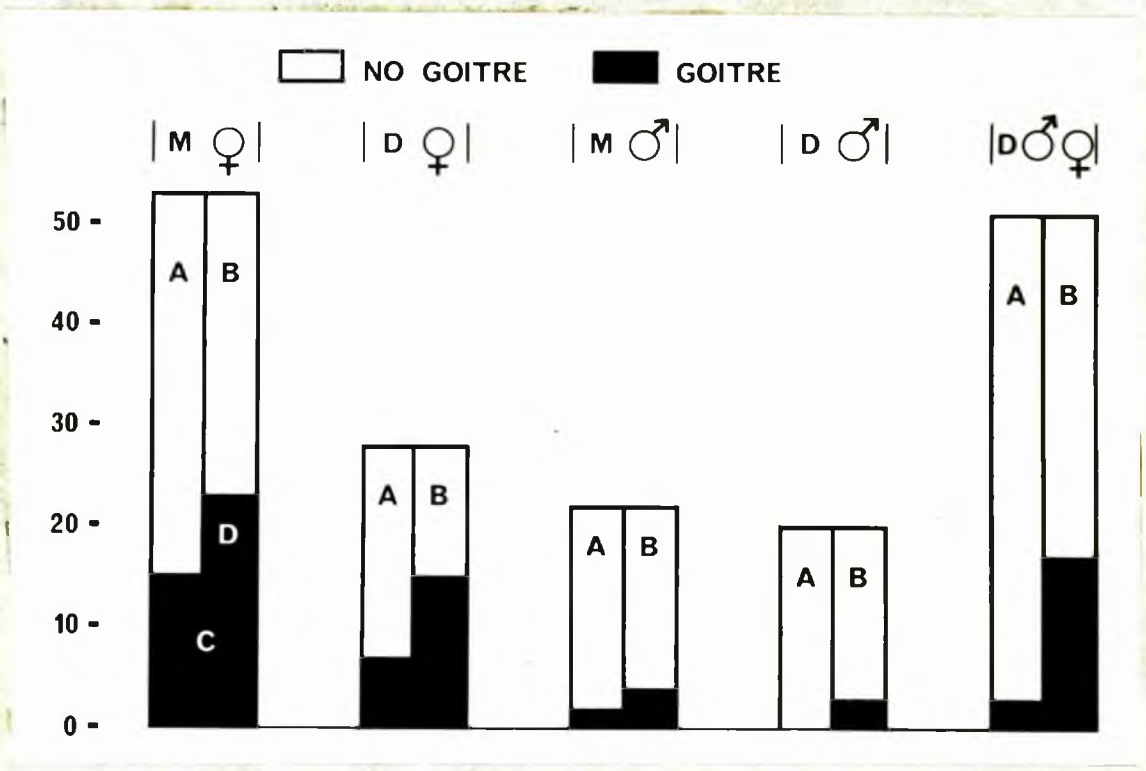

FIGURE 2 Concordance and discordance rates for goitre in 174 twin pairs. The 5 categories of zygosity are represented. M = monozygosity, Black D = dizygotic). A and B represent twin A and B if a pair. C shows the twins who were concordant for goitre and white D those who were discordant for goitre in the monozygotic female group. Goitre was much commoner among females than among males. The analysis of these results is discussed in the text.

RESULTS

The estimation of the role of heredity and environment in the production of simple goitre from data on 348 individuals (174 twin pairs) together with the calculation of PII for 240 individuals (120 twin pairs) and the analyses of these values in respect of age, sex, goitre class, etc., would have been a tedious painstaking task. Accordingly the values for urine iodine and creatinine and plasma creatinine obtained on each individual were fed into a KDF9 computer. The machine calculated PII for each subject and made much of the analysis of the results which will now be presented.

I am grateful to Miss C. Duff of the University of Glasgow Computing Laboratory for making this facility open to me.

TWINS STUDIED Table 1(p.250) shows the zygosity of the 174 twins studied in respect of goitre, their mean ages and age ranges and the number of pairs who had been living apart for more than one year (separated). Each possible category of zygosity is represented and the mean ages and age ranges are comparable. Although the age ranges are wide (12-70 years) it will be seen from the mean ages (which range from 20.6 years in dizygotic male-female pairs to 23.9 years in monozygotic male pairs) that the majority of the twins were in their teens or twenties. An analysis in respect of age distribution is shown in Table 2(p. 241) where the twins have been treated as individuals/

individuals and arranged in age groups: one hundred and sixty four subjects were less than 16 years of age, 80 were between 16 and 20 years, 44 were between 21 and 30 years and 60 were older than 30 years of age. Table 1 also shows the zygosity of the 42 twin pairs who had been separated from each other for more than 1 year.

Similar analyses with respect to age, sex and zygosity for the 120 twin pairs in whom PII was measured are presented in Tables 3 and 4 (p.254- 6).

Goitre Incidence

Table 1 (p.250) shows that goitre was much commoner in females at all ages. The overall goitre incidence (visible and palpable thyroid enlargement) was 35 per cent in females and 10 per cent in males and similar incidences of goitre were noted in the 120 twin pairs in whom PII was measured (33 and 10 per cent respectively). Appendix A (p.268) shows the findings with regard to visible and palpable thyroid gland enlargement for each of the 348 individuals in this study.

Inheritance and Goitre

An assessment of the genetic contribution to goitre formation is given by a comparison of the concordance rate for goitre in the monozygotic pairs (genetically identical) with that in the dizygotic pairs (genetically non-identical). These data are shown in Table 5 (p.258) and Fig. 2. The concordance rates for goitre in the female monozygotic and dizygotic twin pairs were 84.9 and 71.4 per cent respectively. (These rates which represent/

represent total concordance are derived from the sum of the positive and negative concordances shown in Table 5. The number of males with goitre was too low to allow a meaningful interpretation of the data.

Fig. 2 shows the number of twin pairs studied in each category of zygosity (height of histograms). For clarity each pair was considered to consist of twin A and twin B (A and B in the left-hand histogram pertaining to the monozygotic females). It will also be seen that when both twin A and twin B of a pair had visible and palpable thyroid enlargement (goitre) they were concordant for this (C). When only one of the twins had goitre they were discordant for this (D).

An approximate index of the importance of inheritance may be obtained from these results by calculation of the heritability index h (41):

$$h = \frac{\text{per cent monozygotic concordance} - \text{per cent dizygotic concordance}}{100 - \text{per cent dizygotic concordance}} \times 100$$

An h index of 100 per cent suggests that the characteristic under study is wholly genetically controlled whereas a value of zero per cent suggests that heredity has no role in its development. The h value in the female twins in whom goitre was common was 47 per cent, a finding which at first sight suggests that genetic factors do play some role in the aetiology of simple goitre in females in the Glasgow and West of Scotland/

Scotland area.

The heritability index, h, is however only a very crude measure of the genetic contribution to the appearance of a phenotype one of its principle limitations stemming from the underlying assumption that the genetic and non-genetic contributions are additive and sum to one. In fact, interactions between them are often, perhaps always, gross.

In spite of its serious shortcomings the index can serve to summarise very roughly the relative importance of genetic and non-genetic factors in the aetiology of clinical conditions provided that the 95 per cent probability limits can be given. From any set of twin data the probability distribution of h is negatively skewed, hence the quoting of a standard error alone is not adequate. The following procedure, based on likelihoods, gives the probability limits of h to a sufficient degree of accuracy and I am indebted to Dr. J.H. Renwick, Senior Lecturer in Genetics who suggested this method.

Let S = true concordance in monozygotic twins

r = true concordance in dizygotic twins

h = true hereditability

then 1 - S = true discordance in monozygotic twins

and 1 - r = true discordance in dizygotic twins.

Once the sample sizes of the two classes of twins have been fixed, the only observed data are the numbers of concordant pairs in the two groups. It follows from the laws of probability that the likelihood, L, of having observed

a/

a sample of female twins (Table 5 p.258) where 45 and 20 pairs of mono-and dizygotic females respectively were concordant for goitre and 8 and 8 pairs were discordant for goitre is given by

$$L = K S^{45} (1 - S)^{8} r^{20} (1 - r)^{8}$$

where K is a constant.

But since $h = \frac{S - r}{1 - r}$

then $S = r + h - hr$

and $1-S = (1 - r)(1 - h)$

and the equation for the likelihood L, can be rewritten:

$$L = K (r + h - hr)^{45} \left[(1 - r)(1 - h)\right]^{8} r^{20} (1 - r)^{8}$$

thence the likelihood can be expressed in terms of two parameters, h and r, the parameter S being completely determined when h and r are fixed.

The likelihood of this sample can now be evaluated for each of several pairs of h and r values chosen at will. Since, in this example, a priori considerations are difficult to quantitate, they can be simplified to the statement that all true values of h or r are equally likely a priori except for values lying outside the range 0 - 1.0 such values being clearly impossible.

Table 6 (p.260) shows the likelihood for each of the 121 arbitrarily chosen pairs of h and r. Only the relative magnitudes/

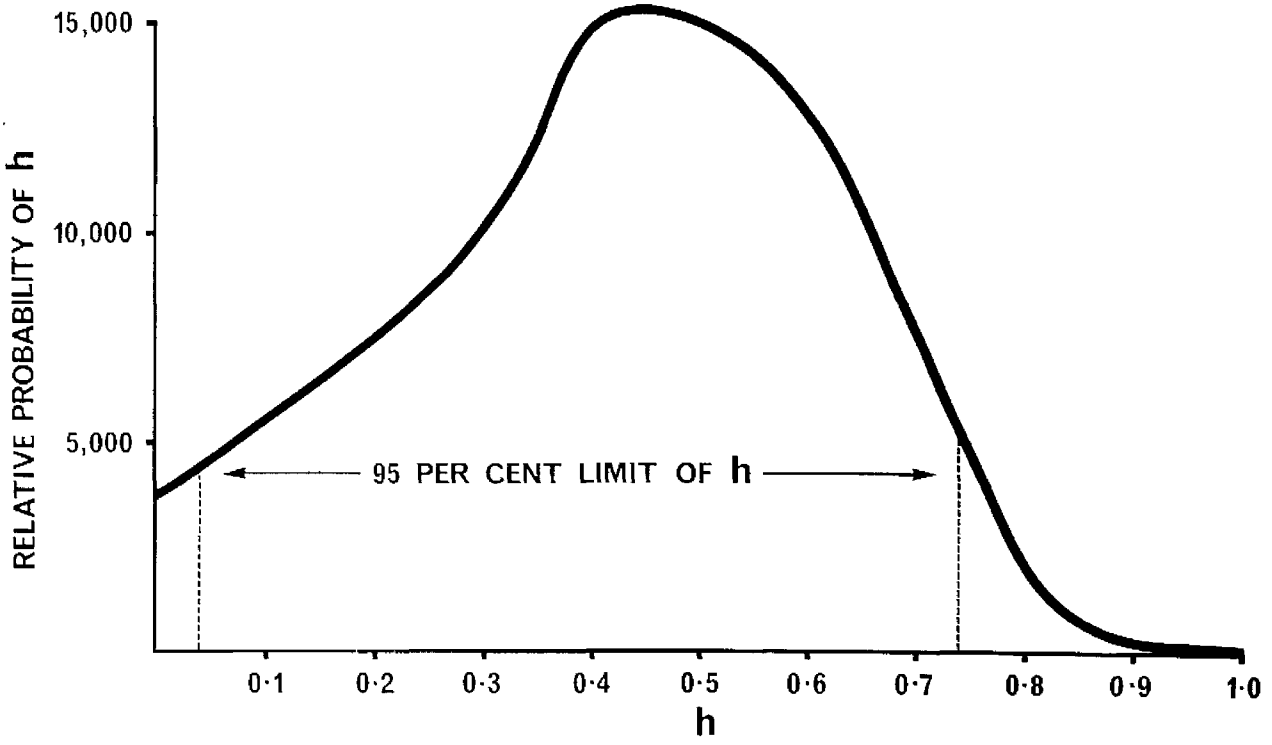

FIGURE 3 Shown are the relative probabilities of h plotted against the values of h. The 95 per cent limits of h were found from this graph to be 4, and 74 per cent.

magnitudes are relevant hence the factor k has been omitted and the uniform *a priori* distribution has been taken to be 1 for all h, x pairs. The values in the table represent altitude determinations on a probability surface although formally one would need to reduce the volume under this surface to 1 (by scaling down) before the word probability would be technically appropriate here. A fuller discussion of the differences between probabilities and likelihoods is given in the third part of the thesis.

The right-hand marginal totals in table 6 give a crude indication of the relative probabilities of different h values, over all values of x. (p.260)

These marginal totals have been plotted in Fig. 3. Marked asymmetry is apparent. In asymmetrical situations such as this it seems appropriate to find the *narrowest* limits which embrace 95 per cent of the area (probability) under the curve. These are also the limits that have equal ordinates at the lower end and the upper end.

Using the property that the limits of h should have equal ordinates, the limits which excluded 5 per cent of the area under the curve were found with the aid of a planimeter to be 0.04 and 0.74 (i.e. 4 and 74 per cent) (Fig. 3). These are thus the 95 per cent limits of h and allow a better interpretation of the h value of 47 per cent.

Goitre and Age/

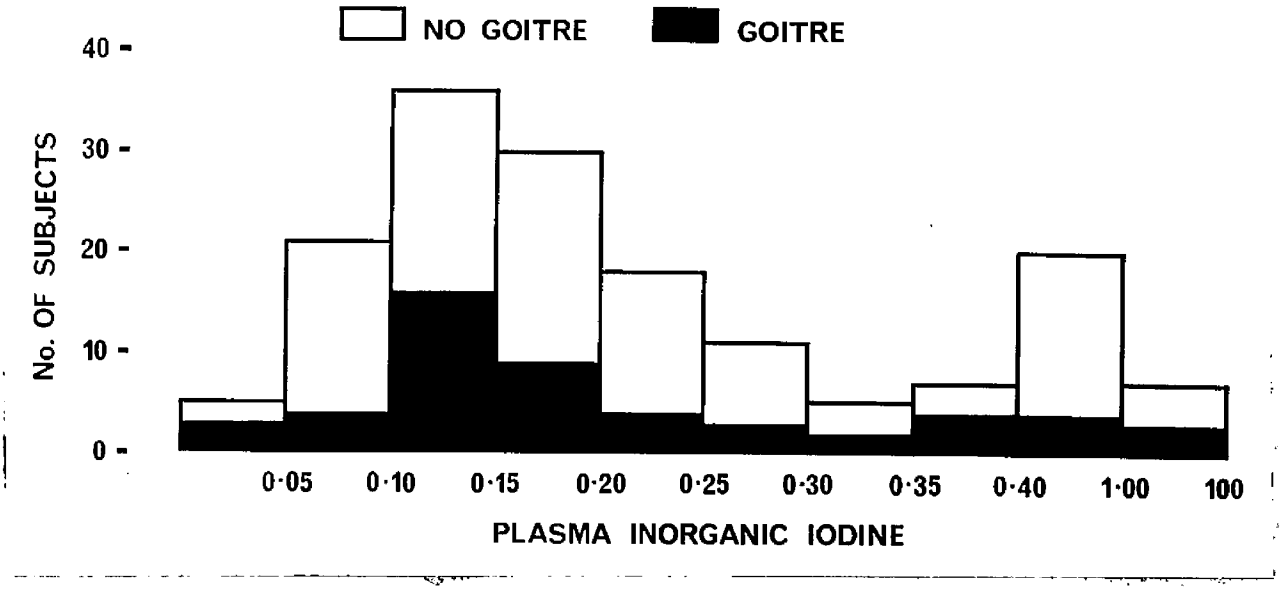

FIGURE 4. Shows the number of goitrous and non-goitrous females in each class of plasma inorganic iodine (PII) level, PII being divided into classes of 0.05 ug per cent. Note that the last two columns on the right hand side of the figure refer to subjects with values between 0.40 and 1.00 and values > 1.00 ug per cent respectively. Goitre was not disproportionately distributed in any one class of PII level.

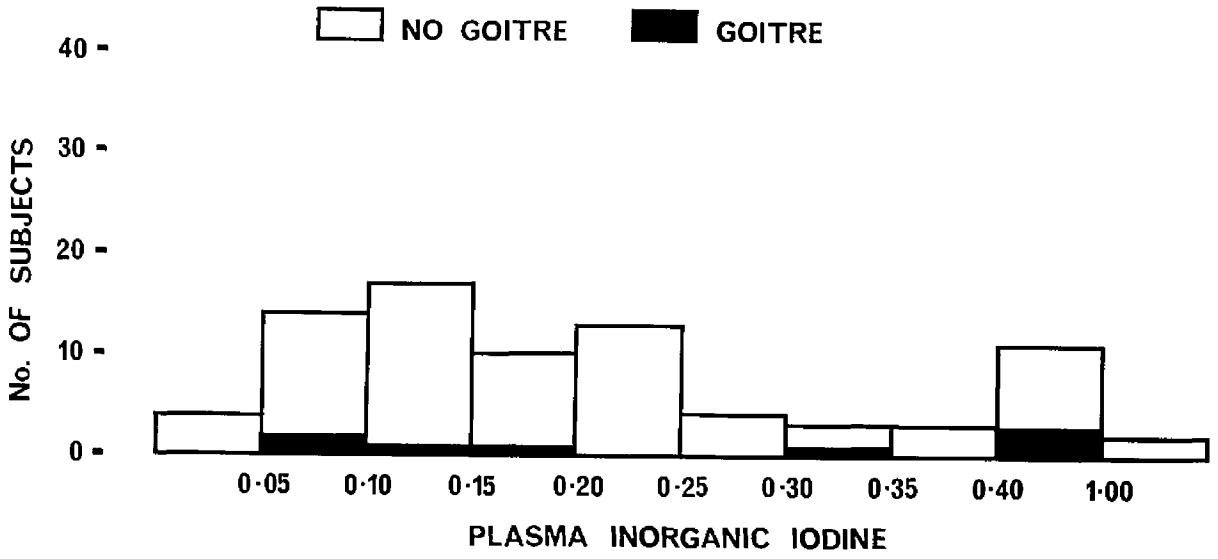

FIGURE 5 Shown are the number of goitrous and non-goitrous males in each class of plasma inorganic iodine (PII) level, PII being divided into classes of 0.05 ug per cent. Note that the last two columns on the right hand side of the figure refer to subjects with values between 0.40 and 1.00 and values > 1.00 ug per cent respectively. Goitre was not disproportionately distributed in any one class of PII level.

Goitre and Age

Table 2 (p.252) shows the number of individuals without goitre compared to those with goitre classified according to age and sex. Goitre was commoner in all age groups in females than in males but was not significantly commoner in any one age range in females compared with all other age ranges.

A similar analysis for the 120 twin pairs in whom PII was measured is shown in Table 4 (p.256).

Goitre and Plasma Inorganic Iodine Levels

PII concentration was >1.0 ug per cent in 9 subjects and in 3 of these it was >2.0 ug per cent. As I specifically wished to detect and evaluate the significance of any possible correlation between low PII values and simple goitre, I felt that it was justifiable to omit these 9 high values from the analysis of the data from the calculation of the means and standard deviations for the remaining 231 individuals in the study. Details of these 9 subjects are shown in Table 7 (p.262).

The results of the analysis are shown in Table 8 (p.264) and Table 9 (p.266) and in Figs. 4 and 5. The individual PII values obtained for each of the 240 subjects are shown in Appendix A (p.268) Table 8 (p.264) shows the mean PII values ($\pm$ standard deviations) in goitrous and non-goitrous males and females. In 103 non-goitrous females the mean PII and standard deviation were 0.24/

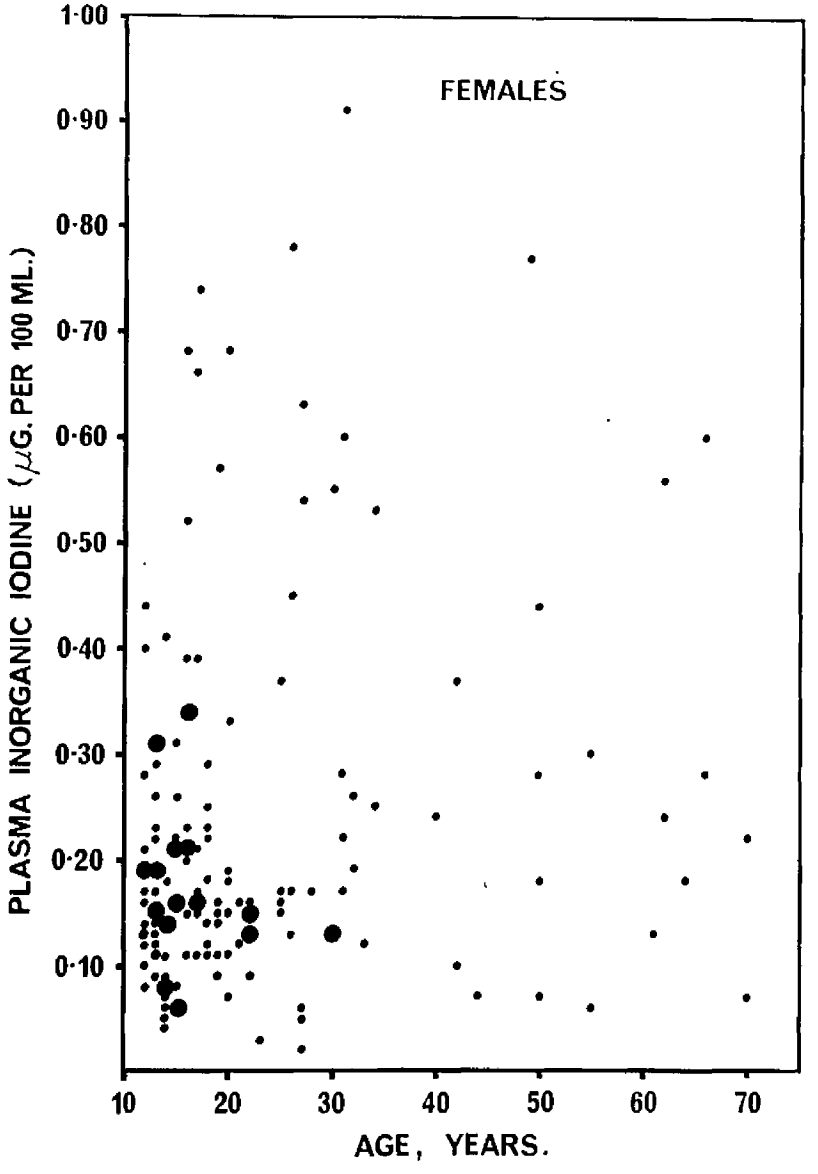

FIGURE 6 A scatterdiagram of plasma inorganic iodine (PII) values plotted against age for female subjects. The larger spots represent more than one individual. There is a correlation between PII and age but this is produced by the lower values found in the 12 - 15 year olds. Above the age of 25 years no correlation between PII and age was found.

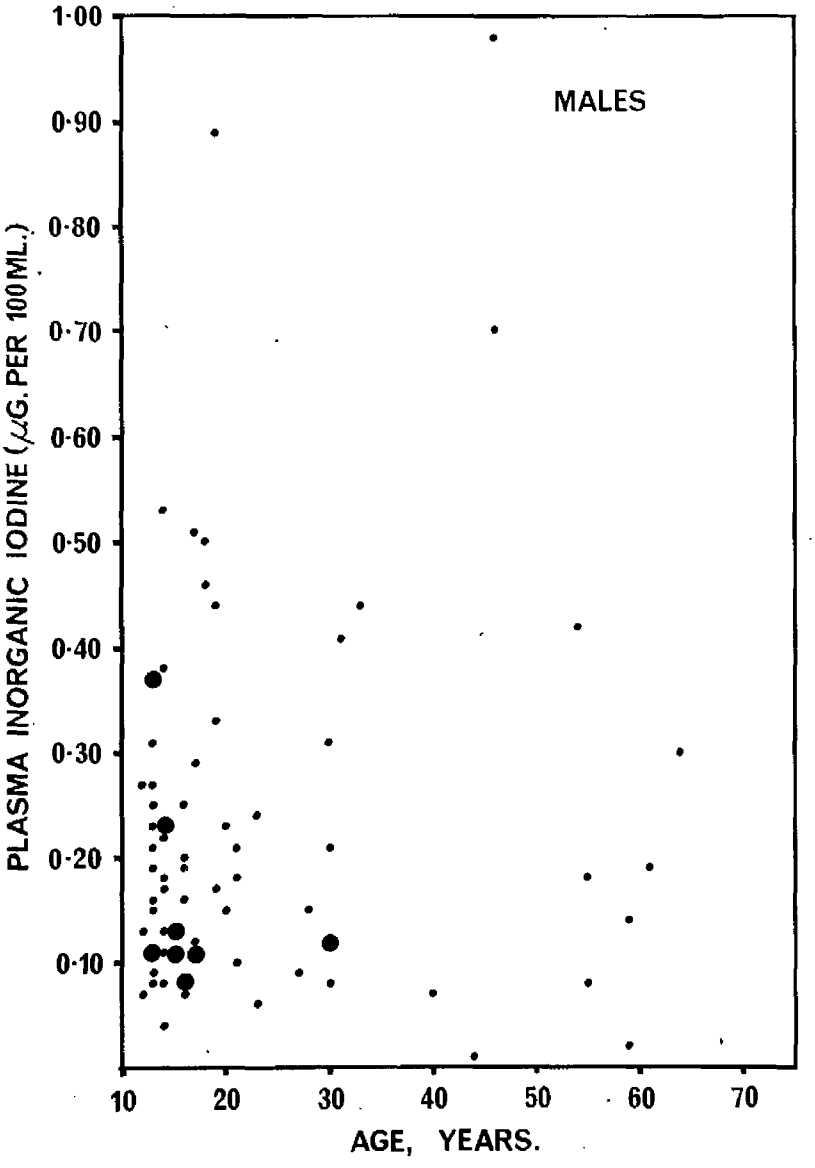

FIGURE 7 A scatterdiagram of plasma inorganic iodine (PII) values plotted against age for male subjects. The larger spots represent more than one individual. A correlation between age and PII values was not so readily demonstrable in males as in females. This may be due to the smaller number of males studied.

0.24 ± 0.179 ug per cent, values which were not significantly different from those found in 50 goitrous females (0.21 ± 0.099 ug per cent). In the 70 males without goitre the values were 0.21 ± 0.162 ug per cent and in the 8 with goitre, 0.32 ± 0.282 ug per cent. These values were not significantly different. This table also shows that there was no difference between the mean PII values when non-goitrous females were compared with non-goitrous males nor when goitrous males were compared with goitrous females. That goitre is not disproportionately distributed in those with PII values in the lower ranges is shown in Figs. 4 and 5 where histograms representing the numbers of subjects in each PII class are presented.

Plasma Inorganic Iodine and Age

Figs. 6 and 7 show a plot of PII against age for male and female subjects. A significant correlation between these two variables was found in females ($r = .16$ $p < .05$) but not in males ($r = 0.02$). Lower values were found in young female subjects, higher values in older ones. Table 9 shows a more detailed analysis of PII levels and age groups in goitrous and non-goitrous male and female subjects in the age ranges 12 to 15, 16 to 20, 21 to 30 and 30 years. It can be seen that the mean PII of the non-goitrous females under 16 years of age was 0.16 ± 0.085 ug per cent a value which was significantly lower than the mean of 0.29 ± 0.206 in the over 16 year olds ($p < 0.01$). It is likely/

likely that this low mean value in the under 16 year old females is the chief factor responsible for the significant correlation between age and PII because the PII values were very similar in the other age groups (Table 9)(p.266). In addition no significant correlation was found between age and PII when subjects under the age of 25 were excluded from the analysis. Similar considerations apply to the goitrous females although the findings were less clearcut perhaps because the number of individuals was somewhat smaller than in the case of the non-goitrous females. There was a suggestion that the mean PII in the 21 - 30 year old non-goitrous males was low but the number of observations in this class was only 10.

Antithyroid autoantibodies

Tests for serum antithyroid autoantibodies in each twin gave positive results in only 16. In none however did the titres, either for autoantibody to thyroglobulin or to thyroid cell "microsomal" antigen reach clinically significant values. These findings suggest that an autoimmune disturbance was not responsible for the occurrence of the small goitres in the twins.

DISCUSSION

The significance of the results of this study hinge on the definition of the term 'goitre' and whether or not one accepts that visible and palpable thyroid gland enlargement as abnormal. In their early study of goitre Marine and Kimball (30) described a gland just visible at the isthmus and on palpation felt as a thickened band across the isthmus as an incipient goitre. The World Health Organisation criteria of goitre (51) list visibility with the head thrown back and the neck fully extended as Grade 1 thyroid enlargement. Grade 2 enlargement is said to occur when the goitre is easily visible in the normal position. Palpation is said to be helpful in "determining the mass of the gland but is not needed for diagnosis". Crooks et al (44) used the criteria of visibility and palpability of thyroid tissue in deciding whether goitre was present or absent. A quantitative, all - or - none definition such as has been used by these workers and in the present study does have an advantage over definitions based on a clinical estimate of gland mass in which the criteria for goitre, although more stringent are nevertheless arbitrary and subject to significant observer error as discussed by Kilpatrick et al (4). Although the thyroid had to be unequivocally palpable and visible in the present study, the majority of the twins had small goitres and it seems reasonable to conclude that I/

I have been mainly studying what Maxine and Kimball would have called "incipient goitre".

The high incidence (35 per cent) of goitre in females almost is identical with the figure reported by Crooks et al (44) (37 per cent) employing the same criteria which I have used for the definition of goitre, in a study of non-pregnant women in their reproductive years in the North East of Scotland. These figures are much higher than those reported by Kilpatrick et al (4) who used similar criteria in a survey of subjects from a general practice in Ormiston, East Lothian (4.3 per cent in women). These differences are probably due to two factors. Firstly a true geographical variation in goitre prevalence and secondly differences in goitre definition between the studies, for in the final analysis the definition of a goitre must always be an extremely subjective one as no one can accurately measure thyroid size clinically. It is not likely that the incidence of goitre was influenced by departures from true random sampling in this study such as a relative excess of female and of monozygotic twins, unavoidable in twin sampling (27) because the ascertainment campaign which I used to collect twins did not mention goitre. The probability that the twins were of an unusually co-operative nature and of above average intelligence is also not likely to have any relevance to the incidence of goitre: there is no/

no reason to suspect that healthy twins are more prone to goitre formation than single births.

It has been suggested that simple goitre is thyroid hypertrophy initiated and maintained by an intrinsic and as yet unidentified stimulus (52). This factor has been considered to be genetic (1) and the hypothesis that individuals who develop simple goitre are intrinsically predisposed by inheritance to develop thyroid hypertrophy is not new (9) and has recently been readvocated by a number of different workers (53-55). However only a small minority of patients with simple goitre have so far been shown to have genetically determined defects in thyroid hormone synthesis which might lead to goitre formation (10). The preponderance of simple goitre in females compared with males (Table 2 p.252) raises the possibility that a sex-linked factor may be of importance in the production of simple goitre. Sex-linked factors, however, may be genetic or environmental. The finding that in the females the hereditability coefficient h was 47 per cent with 95 per cent limits of 4 and 74 per cent suggests that genetic factors do exist and are of importance in the initial development of the small goitres I have described in females in the Glasgow and West of Scotland area.

The/

The PII values in this predominantly young population are approximately 0.05 ug higher on average than the values reported by Wayne's group in Glasgow. These authors reported a mean PII value of 0.19 ug in 33 normal subjects (56). This compares with the mean value of 0.24 ug in 103 non-goitrous female individuals in the present investigation. Although the techniques used for PII estimation were different in each study probably the main factor contributing to the observed differences in PII levels is that I studied the twins in the non-fasting state whereas Wayne et al studied their patients fasting. The lack of correlation of PII level with goitre shown in Table 9 (p.266) and Figs. 4 and 5 suggests very strongly that the 'incipient goitre' which I have been studying is not caused by iodine deficiency and that factors other than this are of primary importance in its development. These conclusions are not necessarily contrary to the findings of Wayne et al (56) or to my own findings reported in section 2 that some patients attending hospital with simple goitre in Glasgow have a low PII. These patients have a different type of thyroid enlargement from that which I found in this study. Their glands are often nodular and are very much larger than the small diffuse thyroid enlargements seen in the twins and it is likely that the goitres seen in hospital out-patient clinics and in the twins I have studied may be two distinct entities.

The/

The possibility does exist however that the larger goitres represent a failure of the smaller ones to regress whether due to the continuing action of an unidentified stimulus to thyroid gland hypertrophy or due to the appearance of another stimulus such as iodine deficiency. If the first possibility were correct however and larger goitres were produced by the continuing action of an unidentified stimulus to thyroid gland hypertrophy the low PII values which have been described in association with these goitres could be due to rather than the cause of increased thyroid activity as Vought et al (57) have suggested. The data however neither confirm nor refute this possibility.

The finding of a significantly lower PII in the female 12 to 15 year olds, compared with those aged 16 years and over confirms the findings of Malvaux et al (58,59) who described lower PII values in 26 adolescents (defined as 10 to 15 year olds) than in young adult controls. In addition my data suggests that the positive correlation reported by Alexander et al (60) between PII and age in 37 females is produced principally by the lower values found in young people because I did not find a significant correlation between these two variables in females over the age of 25 years. It has been suggested (61) that the increased thyroxine turnover rate/

rate which has been described to occur in adolescence (61,62) might result in increased thyroxine production and that this in turn might produce a "primary hyperactivity of the thyroid gland" which produces a low PII. The data in this study is not sufficient to confirm that this was the reason for the lower PII value in the adolescent females but does support the finding of Alexander et al that there are differences between males and females with regard to stable iodine metabolism (60).

In conclusion, although neither genetic transmission nor iodine deficiency has been found to be of prime importance in the young people with small simple goitres whom I studied, a clue to the aetiology of this condition may well lie in the marked preponderance of goitre in females. This suggests that non-genetic sex-linked female factors such as endocrine or metabolic environment may at least initiate, and perhaps maintain thyroid enlargement independently of iodine deprivation.

SUMMARY

The causes of simple goitre in this country are still not clear. Some clinicians believe that an inherited predisposition to goitre formation provoked by a relative deprivation of dietary iodine may be important (9). Some hold that minor inherited defects in thyroid hormone synthesis may be important (10) while others believe that dietary deficiency of iodine may play a part in goitre formation (7). As the population in this country is composed of individuals and families who are genetically heterogeneous there are difficulties in assessing the roles of heredity and environment in simple goitre formation. In the present study some of these difficulties were circumvented by the application of the twin study method. One hundred and seventy four healthy twin pairs from the west of Scotland were examined for goitre (visible and palpable thyroid enlargement) and the concordance rates for goitre (both twins having or not having a goitre) were compared in monozygotic (genetically identical) and dizygotic (genetically non-identical) twin pairs. The result of this comparison suggested that genetic factors were implicated in the aetiology of simple goitre in females but were not of primary importance. Goitre was commoner in females than in males/

males and was found most often in females between the ages of 12 and 20 years.

Plasma inorganic iodine (PII) values were measured in some of the twins by the I/Cr ratio method. Each pair of twins was then considered as two individuals for the purposes of comparing PII values with the occurrence of goitre. No correlation was found between these two variables. In particular goitre was not found to be disproportionately distributed in females with the lower ranges of PII. An interesting finding was that female adolescents (defined as 12 to 15 years) had slightly but significantly lower PII values than those > 15 years of age. This finding had been noted previously by others in a much smaller number of subjects (58,59). The results suggest that non-genetic sex-linked factors such as endocrine or metabolic environment may initiate and perhaps maintain thyroid hypertrophy independently of iodine deprivation.

REFERENCES

1. Kilpatrick, R. and Wilson, G.M. in The Thyroid Gland Ed. R. Pitt-Rivers and W.R. Trotter, Butterworths London, 1964 p.88.

2. Hughes, D.E., Rodgers, K. and Wilson, D.C. (1959), Brit. med. J. 1,280.

3. Trotter, W.R., Cochrane, A.L., Benjamin, I.T., Miall, W.E. and Exley, D. (1962), Brit. J. Prev. and Soc. Med. 16,16.

4. Kilpatrick, R., Milne, J.S., Rushbrooke, M., Wilson, H.S.B. and Wilson, G.M. (1963). Brit. med. J. 1,29.

5. O'Shea, E.M. (1946), Irish J. med. Sci. No.251, 749.

6. Kelly, F.C. and Snedden, W.W. in Endemic Goitre, World Health Organisation, Palais des Nations, Geneva, 1960, p.27 ff.

7. Wayne, E.J., Koutras, D.A. and Alexander, W.D. 1964, Clinical aspects of iodine metabolism, Blackwell Scientific Publications, Oxford. p.107.

8. Spence, A.W. (1952), Brit. med. J. 2,529.

9. Brain, W.R. (1927), Quart. J. Med. 20,303.

10. McGirr, E.M. in Clinical Endocrinology I, Ed. E.B. Astwood, Grune and Stratton Inc. New York (1960), p.133 ff.

11. Galton, F (1875), J. roy. Anthrop. Inst. 5,391.

12. Penrose, L.S.(1959,) Outline of Human Genetics. Heinemann, London. p87ff.

13. Gedda, L. (1951), Studio dei Gemelli, Orrizonte Medico, Roma. p.51.

14. Bonnevie, K. and Sverdrup, A. (1926), J. Genet. 16, 125.

15./

15. Crew, F.A.E. (1960),
The Biology of Polytocia (The Maharaja Sayajirao University of Baroda), Baroda, India.

16. Dahlberg, G. (1926),
Twin Births and Twins From a Hereditary Point of View, Bokforlags AB Tidens Tryckeri, Stockholm, p.84.

17. Dahlberg, G. (1931),
Z. Geburtsh. Gynak. 99, 136.

18. Lamy, M. and Frezal, J. (1958),
Proc. X Internat. Cong. Genetics, Toronto.

19. Weinberg, W. (1909),
Arch. Rassenbiol. 6, 470 and 609.

20. von Verschuer, O. (1959),
Genetik des Menschen. Urban und Schwarzenberg, Berlin p. 181.

21. Russell, J.K.R. (1952),
J. Obstet. Gynaec. brit. Emp. 59, 208.

" "

22. Raiha, C. - E. (1959),
Prematuritet. Nord. Med. 69, 819.

23. Scheinfeld, A. and Schachter, J. (1961),
Proc. Second Internat. Conf. Hum. Genetics, Rome.

24. Genesis Chapter 25, v.25.

25. Corney, and Aherne, W. (1965).
Arch. Dis. Child. 40, 264.

26. Osborne, R.H., Adlersberg, D., De George, F.V. and Wang, C. (1959).
Amer. J. Med. 26, 54.

27. Osborne, R.H. and De George, F.C. (1959),
Genetic Basis of Morphological Variation, Harvard University Press. Cambridge, Mass. p.25.

28. Mathers, J.A.L., Osborne, R.H. and De George, F.V. (1961),
Amer. Heart J. 62, 634.

29. Mayer, K. 1962,
Acta. Med. Scand. 172, 401.

30./

30. Sutton, H.E., Vandenberg, S.G. and Clark, P.J. (1962), Amer. J. hum. Genet. 4, 52.

31. Sutton, H.E., De Lamadrid, E.G. and Esterer, M.B. (1962), Amer. J. hum. Genet. 4, 64.

32. Vandenberg, S.G. (1962), Amer. J. hum. Genet. 4, 220.

33. Jarvik, L.F., Kallman, F.J. and Falek, A. (1962), J. Geront. 17, 289.

34. Leonhardt, T. (1962), Acta. genet. (Basel), 12, 251.

35. Jarvik, L.F. and Falek, A. (1962), Cancer (Philad.), 15, 1009.

36. Ostwald, P.F., Freedman, D.G. and Kurtz, J.H. (1962), Folia phoniat. (Basel), 14, 37.

37. Shields, J., Monozygotic Twins Brought up apart and Brought up together, Oxford University Press, London (1962), 264 pp.

38. Gedda, L. and Poggi, D. (1964). Acta. Genet. med. gem. 13, 1.

39. Gedda, L., Brenci, G. (1964), Acta. Genet. med. gem. 13, 105.

40. Cederlof, R., Friberg, L., Jonsson, E. and Lennart, K. (1965), Arch. environ Health, 10, 346.

41. Newman, H.H., Freeman, F.N. and Holzinger, K.J. A Study of Heredity and Environment. Chicago University Press, Chicago (1937), p.17.

42. Holt, S.B. (1961), Brit. med. Bull. 17, 247.

43. Dencker, S.J., Hauge, M., Kaij, L. and Nielsen, A. (1961), Acta. genet. 11, 265.

44. Crooks, J., Aboul-Khair, Turnbull, A.C. and Hytten, F.E. (1964), Lancet, 2, 334.

45. /

45. Broadhead, G.D., Pearson, I.B. and Wilson, G.M. (1965), Brit. med. J. 1, 343.

46. Anderson, J.R., Buchanan, W.W., Goudie, R.B. and Gray, K.G. (1962), J. clin. Path. 15, 462.

47. Buchanan, W.W., Koutras, D.A., Crooks, J., Alexander, W.D., Bruce, W., Anderson, J.R., Goudie, R.B. and Gray, K.G. (1962), J. Endocr. 24, 115.

48. Hare, R.S. (1950). Proc. Soc. Exp. Biol. Med. 74, 148.

49. Farrell, L.P. and Richmond, M.H. (1961), Clin. Chim. Acta. 6, 620.

50. Marine, D. and Kimball, O.P. (1917), Lab. clin. Med. 4,40.

51. Perez, C. Scrimshaw, N.S. and Munoz, J.A. in Endemic Goitre. World Health Organization, Palais des Nations, Geneva, 1960, p.376.

52. Trotter, W.R., Diseases of the Thyroid, Blackwell Scientific Publications, Oxford, 1962, p.98.

53. London, W.T., Koutras, D.A., Pressman, A. and Vought, R.L. (1965), J. clin. Endocr. 25, 1091.

54. Beckers, C., Barsellato, J., Stevenson, C. Gianetti, A., Pardo, A., Bobadilla, P. and De Visscher, M. in Current Topics in Thyroid Research, Ed. C. Cassano and M. Andreoli, Academic Press, New York, 1965, p. 838.

55. Lewitus, Z. and Lubin, E. in Current Topics in Thyroid Research, ed. C. Cassano and M. Adreoli. Academic Press, New York, 1965, p. 843.

56. Alexander, W.D., Koutras, D.A., Crooks, J., Buchanan, W.W., Macdonald, E;M., Richmond, M.H. and Wayne, E.J. (1962), Quart. J. Med. NS 31, 281.

57. Vought, R.L. Maisterrena, J.A., Tovar, E. and London, W.T. (1965). J. clin. Endocr. 25, 551.

58./

58. Malvaux, P. Beckers, G. De Visscher, M. (1965), J. clin. Endocr. 25, 877.

59. Malvaux, P. Ponchon, G., Beckers, G. and De Visscher, M. Current Topics in Thyroid Research, 1965. ed. Cassano, C. and Andreoli, M. Academic Press, New York, p. 237.

60. Alexander, W.D., Koutras, D.A., Hanson, R.Mac. and Wayne, E.J. (1964). J. clin. Endocr. 24, 851.

61. Beckers, G., Malvaux, P. and De Visscher, M. (1966), J. clin. Endocr. 26, 202.

62. Rang, W., Cancuyco, G.P. and Heald, F.P. (1965), Pediatrics, 35, 76.

PART 2

INTRODUCTION

This part of the thesis describes the use of a phenomenon known as the iodide inhibition phenomenon in the diagnosis of Hashimoto's disease from simple goitre and simple goitre from toxic goitre. In addition studies on the mechanism of the phenomenon in various thyroid states are presented.

The part is in three sections. The first section describes the phenomenon of iodide inhibition and describes work done by others prior to the studies presented in this thesis. This section then gives details of the studies I undertook to exploit the potential usefulness of the phenomenon as a test for the differentiation of simple goitre from Hashimoto's disease and simple goitre from thyrotoxic goitre. Abnormalities of radioiodine metabolism are known to occur in patients with Hashimoto's disease (1) and when I found that these patients reacted abnormally to the pharmacological doses of iodides used in the iodide inhibition test it seemed logical to see whether patients with other conditions known to be associated with abnormalities of radioiodine metabolism (2) also reacted in an abnormal fashion to the iodide inhibition test. This section of this part of the thesis deals/

deals with this point and shows that patients submitted to thyroidectomy or treated by radioiodine for thyrotoxicosis exhibit the phenomenon of iodide inhibition.

The second section of this part details the attempts I made to explain those interesting findings. In it I shall outline studies of the metabolism of stable iodine (as opposed to radioiodine) before and during the iodide inhibition test which shows that there are at least two different mechanisms responsible for the phenomenon of iodide inhibition.

For the sake of completeness in detailing my work on the phenomenon of iodide inhibition the third section describes some further observations on patients and some animal experiments which were undertaken to explain one of these mechanisms in greater detail.

(1) Buchanan, W.W., Koutras, D.A., Alexander, W.D., Crooks, J., Richmond, M.H., Macdonald, E.M. and Wayne, E.J. (1961). J. clin. Endocr. 21, 806.

(2) Eckert, H., Green, M., Kilpatrick, R. and Wilson, G.M. (1960). Clin. Sci. 20, 87.

PART 2

SECTION 1

THE USE OF THE PHENOMENON OF IODIDE INHIBITION IN THE DIAGNOSIS OF HASHIMOTO'S DISEASE AND SIMPLE GOITRE WITH SOME OBSERVATIONS ON THE OCCURRENCE OF THE PHENOMENON IN SOME OTHER STATES OF THYROID FUNCTION

Following the work of Plummer (1), Stanley (2) and Childs et al (3) on the effect of varying doses of stable iodide on the thyroid gland, Feinberg and his associates (4) introduced the iodide inhibition test into clinical practice. These workers showed that the 24 hour ^{131}I uptake of the thyrotoxic thyroid was significantly depressed from the control value when 2 mg of potassium iodide (KI) carrier was administered with the tracer dose of ^{131}I. They termed this phenomenon "iodide inhibition". This inhibition of uptake was not seen in normal thyroid glands.

Subsequently Paris et al (5,6) demonstrated that the phenomenon of iodide inhibition was seen in Hashimoto's disease and in iodide goitre. None of these workers was able to explain the mechanism of these findings.

The simplicity of the iodide inhibition test which Feinberg et al propounded makes it an especially attractive means of distinguishing the patient with simple goitre from the patient with thyrotoxic goitre or of identifying the patient with Hashimoto's disease.

The studies reported in this section of the thesis were undertaken first to investigate the usefulness of the iodide inhibition test in distinguishing Hashimoto's disease from simple goitre and simple goitre from toxic goitre; second to see if iodide inhibition occurred in other conditions where there/

there is known to be alteration of ^{131}I kinetics because if this were so the diagnostic usefulness of the test might be curtailed.

MATERIALS

One hundred and eleven patients were studied (Table 1 p.300). Eleven patients, 10 female, 1 male, mean age 41.3 years with no evidence of thyroid, renal or other endocrine disease served as controls. Twenty two patients were accepted by clinical and laboratory study to have simple goitre. The mean age of this group was 34.3 years; 21 were female. Twenty five patients had Hashimoto's disease, this diagnosis being arrived at on clinical grounds supplemented by the finding of a positive precipitin test for circulating autoantibody to thyroglobulin (7) and or a positive complement fixation test for "antimicrosomal" thyroid autoantibodies (8) together with characteristic ^{131}I studies. (Less than 80 per cent of the 48 hour plasma protein-bound iodine ($PB^{131}I$) being butanol extractible (9,10) and or a discharge of at least 12 per cent of accumulated radioactivity from the thyroid gland following the administration of $KClO_4$ (10)). Twenty four of these patients were female the mean age being 42.5 years. There were 11 patients who were thyrotoxic both clinically and by ^{131}I studies (24 hour thyroidal ^{131}I uptake and 48 hour $PB^{131}I$), comprising 9 females and 2 males, mean age/

age being 31.6 years. Twenty three patients, 15 females and 8 males previously thyrotoxic had been rendered euthyroid by ^{131}I therapy and had been euthyroid for at least 1 year at the time of study. The mean age of this group was 49.4 years. Thirteen patients had undergone thyroidectomy for thyrotoxicosis 1 year or more before study and all were euthyroid. The mean age of this group of 10 females and 3 males was 39.2 years. A further 5 patients, all females, had undergone thyroidectomy for simple goitre; their mean age was 35.3 years. 1 male patient aged 29 years had Pendred's syndrome.

METHODS

Measurements of the 24 hour thyroidal ^{131}I uptake and 48 hour plasma PB^{131}I levels were made before and after 2 mg KI had been added to a 25 uc tracer dose of ^{131}I. The thyroid gland ^{131}I uptake was monitored using a $1\frac{3}{4}$" diameter by 2" thick thallium activated sodium iodide crystal coupled to an IDL 1700 C scaler-timer. The thyroid was viewed using a lead collimator which has an internal diameter of 4.5 cm. at the face of the crystal expanding to 7 cm. in a length of 12 cm. The crystal - thyroid distance was 20 cm. The PB^{131}I was measured in a well-type scintillation counter after the serum had been passed through an ion-exchange resin column (Amberlite resin IRA - 400 (Cl)) to remove inorganic radioiodine/

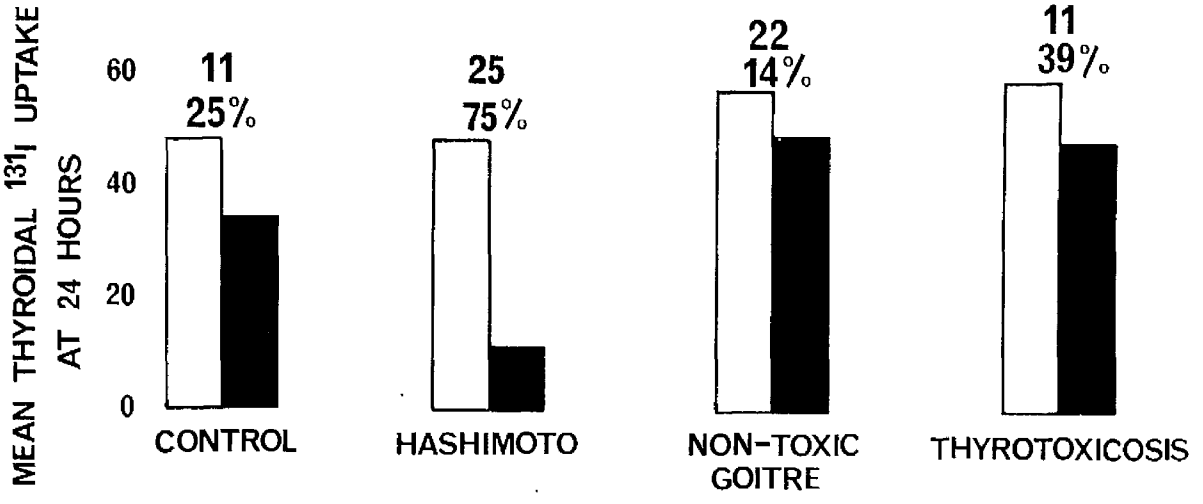

FIGURE 1 Shown are the control mean 24 hour thyroidal ^{131}I uptake values (open histograms) and the mean 24 hour thyroidal ^{131}I uptake values when 2 mg KI was given with the oral tracer ^{131}I dose (black histograms) in a variety of thyroid conditions. Percentage figures refer to the percentage inhibition of ^{131}I uptake produced by KI as discussed in the text. The figures above the percentages refer to the number of patients with each condition. The term non-toxic goitre refers to patients with simple goitre.

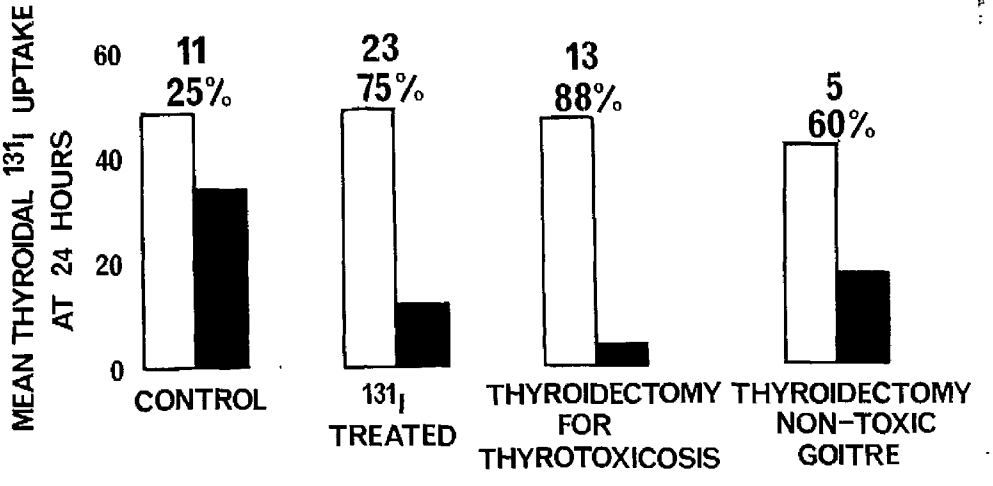

FIGURE 2 Shown are the control mean 24 hour thyroidal ^{131}I uptake values (open histograms) and the mean 24 hour thyroidal ^{131}I uptake values when 2 mg KI was given with the oral tracer ^{131}I dose (black histograms) in a variety of thyroid conditions. Percentage figures refer to the percentage inhibition of ^{131}I uptake produced by KI as discussed in the text. The figures above the percentages refer to the number of patients with each condition. The term non-toxic goitre refers to patients with simple goitre.

radioiodine from the sample. The counter had a 2" diameter by a 1" thick crystal with $\frac{3}{4}$" diameter by $\frac{1}{2}$" deep well.

The second studies after the addition of iodide were performed 2 weeks after the initial test, the blood and thyroid gland being checked for residual radioactivity before the second ^{131}I tracer dose was given.

The percentage inhibition of thyroidal ^{131}I uptake (or of plasma PB^{131}I) was calculated from the formula of Feinberg et al (4)

$$(1) \quad \frac{\text{First uptake} - \text{Second uptake}}{\text{First uptake}} \times 100$$

The actual fall in ^{131}I uptake was also recorded because, if the first ^{131}I uptake is relatively low, it requires but a small degree of inhibition of the second uptake to make the percentage inhibition of uptake quite large.

RESULTS

Twenty four hour thyroidal ^{131}I

The effect of 2 mg KI on the gland uptake is illustrated in Table 1 (p.300) and in Figs. 1 and 2. The individual results obtained for each of the 111 patients studied are shown in Appendix A (p.307). The control subjects showed a mean inhibition of uptake of 25 per cent ranging from + 41 per cent (meaning that in some patients the/

the uptake after KI was higher than before it) to 50 per cent. Standard deviation was 29 per cent. In patients with simple goitre the mean inhibition of uptake was 14 per cent ranging from + 40 to 51 per cent, the standard deviation being 25 per cent. The inhibition in the simple goitre group is not significantly different from the control group. In assessing significance of the results Student's t test has been performed as described in H.M. Stationary Office booklet on Industrial Experimentation (11).

In the group with untreated thyrotoxicosis some inhbition was demonstrated in all patients but although this was as great as 85 per cent, it was also as little as 6 per cent. The mean inhibition was 39 per cent and the standard deviation was 22 per cent in this group. In the patients with Hashimoto's disease a substantial inhibition of uptake was observed in every case ranging from 56 to 95 per cent the mean and standard deviation being 75 ± 11 per cent. The mean inhibition of uptake in patients with thyrotoxicosis was not significantly different from the control group ($P > 0.10$) but was more than those with simple goitre ($P < 0.02$). The mean inhibition of uptake of the patients with Hashimoto's disease was on the other hand highly significantly different both from that of the control group ($P < 0.0001$) and from that of the patients with simple goitre ($P < 0.0001$).

Almost/

Almost all the patients rendered euthyroid by radio-iodine treatment showed a marked inhibition of uptake after KI: the mean and standard deviation were 75 ± 22 per cent, the range 19 to 97 per cent. Similarly in the patients who had undergone thyroidectomy for thyrotoxicosis a striking degree of inhibition of uptake was encountered ranging from 68 to 100 per cent the mean and standard deviation being 88 ± 10 per cent. Patients after thyroidectomy for simple goitre showed a mean inhibition of uptake of 60 ± 11 per cent with a range of from 42 to 70 per cent. The mean inhibition of uptake in the last three groups of patients mentioned was significantly different from the control group in each case ($P < 0.0001$, $P < 0.0001$ and $P < 0.001$, respectively).

48 hour plasma $PB^{131}I$

The effect of 2 mg KI on the 48 hour plasma $PB^{131}I$ level is shown in Table 2(p.304) and Fig. 3. The individual results obtained for each of the 111 studied are shown in Appendix A (p.307). In control subjects and in the patients who had been submitted to surgery for simple goitre there was no significant level of $PB^{131}I$ detectable in the plasma at 48 hours. Therefore, it was not possible to measure inhibition of this index in these patients. The effect of the iodide load was found in most cases to be very much less clear/

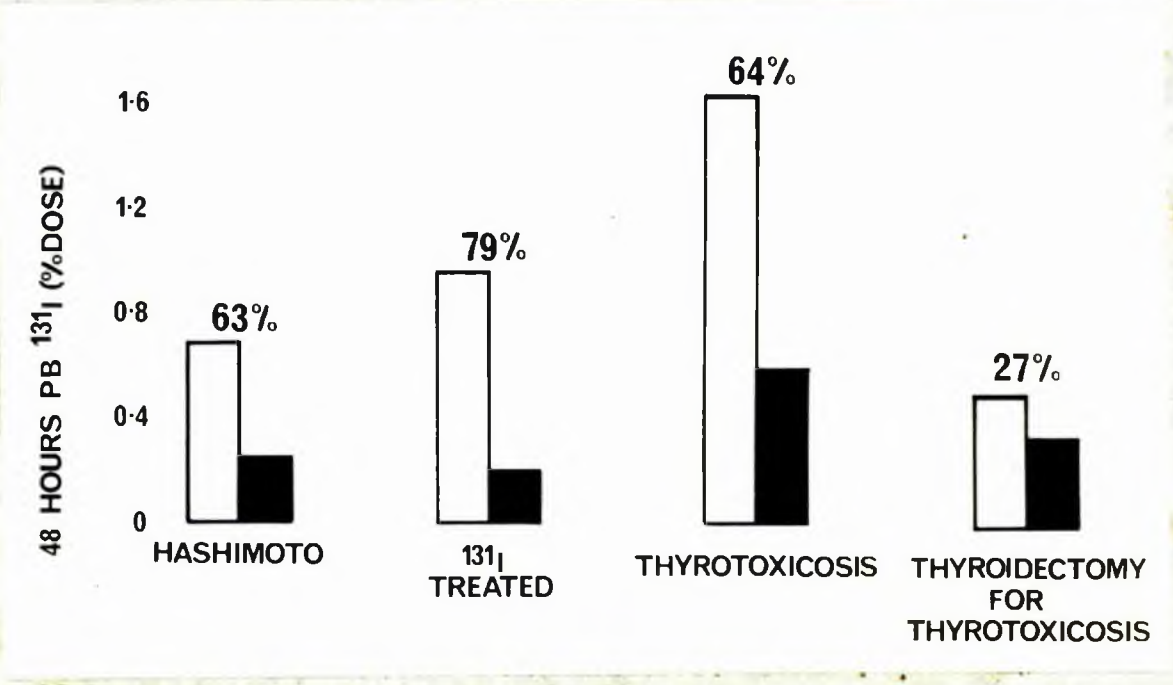

FIGURE 3 Shown are the control mean $PB^{131}I$ levels 48 hours after ^{131}I administration expressed as percentage of administered dose (open histograms) and the $PB^{131}I$ levels when 2 mg KI was given with the tracer ^{131}I dose (black histograms) in a variety of thyroid conditions. The percentage figures refer to the percentage inhibition of $PB^{131}I$ as discussed in the text.

clear cut than was the effect on thyroidal ^{131}I uptake.

Thus the mean PB^{131}I was reduced by 54 ± 41 per cent in the patients with Hashimoto's disease. This figure is lower than the mean fall which occurred in the thyroidal ^{131}I uptake in this group.

The mean fall in PB^{131}I of 79 ± 19 per cent (range 31 to 100 per cent) in patients rendered euthyroid by ^{131}I therapy was similar to the fall which had occurred in ^{131}I uptake in this group. The mean inhibition of 64 ± 28 per cent in the thyrotoxic group was somewhat greater than the mean inhibition of ^{131}I uptake in these patients.

There was, however, a striking discrepancy in the degree of inhibition of the two measurements in the patients submitted to thyroidectomy for thyrotoxicosis. Although the mean inhibition of ^{131}I uptake was 88 ± 10 per cent the mean fall in PB^{131}I level was only 27 ± 38 per cent.

DISCUSSION

These results confirm the observation of others (5) that the phenomenon of iodide inhibition occurs in Hashimoto's disease. In addition they make it possible to define an abnormal response to the 2 mg KI load and thus put the phenomenon on the firmer basis of a test. In no patient out of the 11 controls was inhibition of 24 hour thyroidal ^{131}I uptake greater than 55 per cent seen. However 24 of the 25 patients with Hashimoto's disease were found to demonstrate/

demonstrate this degree of iodide inhibition. It is probable that if one wishes to assess the diagnostic efficacy of the test the behaviour of the patients with Hashimoto's disease should be compared not to the behaviour of the control group but to that of the group with simple goitre because the patient with Hashimoto's who presents diagnostic difficulty often has a goitre. None of the patients with simple goitre however demonstrated iodide inhibition greater than 55 per cent. These observations suggest that it is extremely likely that a patient with a non-toxic goitre in whom the diagnosis lies between simple goitre and Hashimoto's disease, who exhibits an inhibition of ^{131}I uptake greater than 55 per cent, has Hashimoto's disease. Conversely such a patient not demonstrating iodide inhibition of this order is likely to have a simple goitre.

The results of this study suggest therefore that the phenomenon of iodide inhibition may be a useful test for Hashimoto's disease. Two qualifications to this statement must be added. Firstly the value of any new test can only be judged with certainty on the results it gives in the clinically difficult case. Secondly, as there is no test which is invariably positive in patients with Hashimoto's disease (12,13) it is not unlikely that with further experience of the procedure more patients with Hashimoto's disease may be/

be found who do not give a positive result to the techniques. As with any new test only increasing experience with a la rger number of patients over a number of years can answer these points.

The results of this study also show that the phenomenon of iodide inhibition is not consistently observed, in this country at any rate, in patients with thyrotoxicosis. Only 2 of the 11 patients with thyrotoxicosis satisfied my criterion of a positive response to the iodide inhibition test. Feinberg et al (4) who took a figure of 50 per cent inhibition of uptake as the criterion of an abnormal result found a consistent response however in his thyrotoxic patients in the U.S.A.: all exhibited the phenomenon of iodide inhibition. It is not feasible that differences in the technique used in performing such a simple procedure as the iodide inhibition test could be responsible for the marked differences in results between the two studies. One can only speculate that a possible explanation for the diffences found might conceivably be differing dietary iodide intake in the two groups studied.

Thus in the U.S.A. where iodide supplements are often added routinely to table salt (14) plasma inorganic iodine levels may be high and the intrathyroidal iodine content of the thyrotoxic gland may be higher than that of/

of the thyrotoxic thyroid in Scotland where there is no such routine dietary iodide supplementation (15) and where it is known that plasma inorganic iodine levels are lower than in the U.S.A. (16). The thyroid with a lower intrathyroidal iodine store may accumulate much more of the iodide load presented in the iodide inhibition test than will the thyroid with the higher intrathyroidal iodine content. If a greater proportion of the $^{127}I/^{131}I$ mixture were accumulated in the thyroid gland, less inhibition of ^{131}I uptake would be seen. This might explain why my patients showed less inhibition of ^{131}I uptake than did the patients studied by Feinberg et al. This is speculation however and I have no direct evidence to support it. The practical aspect to these results however is that they show that the iodide inhibition test is not of value in the diagnosis of simple goitre from toxic goitre in this country.

The inhibition of thyroidal ^{131}I uptake produced by 2 mg KI is just as striking in patients rendered euthyroid by ^{131}I therapy as by operation as it is in those patients with Hashimoto's disease, and 4 out of the 5 patients studied after thyroidectomy for simple goitre exhibited iodide inhibition. From the clinical standpoint it is not probable that patients after thyroidectomy would be mistaken for patients with Hashimoto's disease. It is possible,/

possible, however, that patients who have previously been treated by ^{131}I therapy are on occasion tentatively diagnosed as having Hashimoto's disease. It is being increasingly realised that there is an appreciable risk of hypothyroidism after ^{131}I therapy (17 - 22) and a patient who presents with possible mild hypothyroidism, the post ^{131}I radiation remnant of a once thyrotoxic goitre and a raised 48 hour plasma PB^{131}I level might be misdiagnosed if he or she did not give a clear history of ^{131}I treatment. These patients have also occasionally been described to have circulating antithyroid autoantibodies in their blood (8,23 - 26). If one were confronted with this possible differential diagnosis, it is clear that the iodide inhibition test would have no value in distinguishing between the two conditions.

The degree of inhibition of 48 hour plasma PB^{131}I levels produced by 2 mg. KI given with the tracer dose in general was found to run parallel with the inhibition of thyroid ^{131}I uptake with the exception of the thyroidectomy remnant. Here the mean inhibition of ^{131}I uptake of 88 per cent contrasted sharply with the mean PB^{131}I inhibition of 27 per cent. No obvious explanation suggests itself for this discrepancy. As the inhibitions observed in the PB^{131}I were less clear cut than those obtained in the uptakes it seems reasonable to suggest that only the 24 hour thyroidal ^{131}I uptake need be measured in the test and that the 48 hour plasma PB^{131}I level may/

may be neglected. The test as a consequence becomes even more simple to perform.

It is not possible to hazard an explanation for the phenomenon of iodide inhibition from the observations so far presented. This has also been the opinion of other workers (5,6). The next section of this part of the thesis will therefore present some experiments which I undertook in an effort to explain why some patients exhibit the phenomenon of iodide inhibition.

SUMMARY

Iodide inhibition consists of a reduction in the 24 hour thyroidal ^{131}I uptake greater than 55 per cent of the control value when 2 mg potassium iodide is added to the diagnostic ^{131}I tracer dose. The phenomenon has been studied in 111 patients. Eleven were normal controls, 25 had Hashimoto's disease, 11 were thyrotoxic, 23 had been rendered euthyroid by thyroidectomy, 22 had simple goitre, 5 had had a thyroidectomy for simple goitre and 1 patient had Pendred's syndrome. The results show that iodide inhibition occurs in patients with Hashimoto's disease, patients rendered euthyroid by ^{131}I therapy and patients thyroidectomised for thyrotoxicosis or simple goitre. The phenomenon is sufficiently clear cut in the patients with Hashimoto's disease to serve as a diagnostic phenomenon for it was present in 24 of the 25 patients with Hashimoto's disease and none of the 22 patients with simple goitre. The phenomenon was not sufficiently clear cut in the patients with thyrotoxicosis to allow its use as a test for this condition.

REFERENCES

1. Plummer, H.S. (1923),
J. Amer. Med. Ass. 80, 1955.

2. Stanley, M.M. (1949),
J. clin. Endocr. 9, 941.

3. Childs, D.S., Jr., Keating, F.R., Jr., Rall, E.J.
Williams, M.M.D. and Power, M.H. (1950),
J. clin. Invest. 29, 726.

4. Feinberg, W.D., Hoffman, D.L. and Owen, C.A. (1959),
J. clin. Endocr. 19, 567.

5. Paris, J., McConahey, W.M., Owen, C.A., Woolner, L.B.
and Bahn, R.C. (1960),
J. clin. endocr. 20, 57.

6. Paris, J., McConahey, W.M., Tauxe, W.N., Woolner, L.B.
and Bahn, R.C. (1961),
J. clin. Endocr. 21, 1037.

7. Anderson, J.R., Buchanan, W.W., Goudie, R.B. and Gray, K.G.
(1962),
J. clin. Path. 15, 462.

8. Buchanan, W.W., Crooks, J., Alexander, W.D., Brass, W.,
Anderson, J.R., Goudie, R.B. and Gray, K.G. (1962),
J. Endocr. 24, 115.

9. Owen, C.A., Jr., and McConahey, W.M. (1956),
J. clin. Endocr. 16, 1570.

10. Murray, I.P.C. and McGirr, E.M. (1960),
Brit. med. J. 1, 838.

11. Brownlee, K.A., (1957),
Industrial Experimentation, H.M. Stationary Office,
London. Ed. 4 p.34.

12. Buchanan, W.W., Harden, R. McG. and Clark, D.H. (1965),
Brit. J. Surg. 52, 430.

13. Boyle, J.A., Greig, W.R., Franklin, D.A., Harden, R.McG.,
Buchanan, W.W. and McGirr, E.M. (1966),
Quart. J. Med. (in press).

14./

14. Holman, J.C.M. and McCartney, W. in
Endemic Goitre. World Health Organisation Monograph Series
No. 44. Geneva, 1960 (p.411).

15. Editorial (1960),
Scot. med. J. 5,361.

16. London, W.T., Koutras, D.A., Pressman, A. and
Vought, R.L. (1965).
J. clin. Endocr. 25, 1091.

17. Beling, U. and Einhorn, J. (1961),
Acta. Radiol. (Stockholm), 56, 276.

18. Dunn, J.T. and Chapman, E.M. (1964),
New Eng. J. Med. 271, 1037.

19. Green, M. and Wilson, G.M. (1964),
Brit. Med. J. 1, 1005.

20. MacGregor, A.G. in The Thyroid and its Diseases.
Ed. A.S. Mason, Pitman Publishing Co. Ltd., 1963, p.19.

21. McGirr, E.M., Thomson, J.A. and Murray, I.P.C. (1964),
Scot. med. J. 9, 505.

22. Editorial (1965),
Lancet, 1, 637.

23. Irvine, W.J., Macgregor, A.G. and Stuart, A.E. (1962),
Lancet, 2, 843.

24. Irvine, W.J. (1964),
Quart. J. exp. Physiol. 49, 324.

25. O'Gorman, P. Staffurth, J.S. and Ballentyne, M.R. (1964),
J. clin. Endocr. 24, 1072.

26. Einhorn, J., Fagreus, A. and Jonsson, J.,
Current Topics in Thyroid Research, Ed. C. Cassano and
M. Andreoli, Academic Press, New York and London, 1965,
p.1137.

PART 2

SECTION 2

STUDIES OF THE MECHANISMS OF OCCURRENCE OF IODIDE INHIBITION

PART 2. SECTION 2.

In the previous section it was shown that iodide inhibition occurs in patients with Hashimoto's disease, in patients thyroidectomised for thyrotoxicosis or simple goitre and in patients rendered euthyroid by ^{131}I. It seemed that studies of stable iodine metabolism might be helpful in explaining the phenomenon because many writers have stressed the importance of measurements of both stable and radioiodine if the full picture of iodine metabolism is to be understood. Riggs (1) has said, "Only by the combined use of radioactive iodine tracers and of chemical methods can a clear picture of the over-all metabolism of iodine be obtained". More recently Wayne and his colleagues have re-stressed the importance of this statement (2) and in a series of papers have demonstrated clearly the value of a knowledge of stable iodine metabolism in the understanding of radioiodine kinetics and the interpretation of radioiodine studies (2 - 6).

I reasoned that the phenomenon of iodide inhibition is most clear cut when one considers inhibition of uptake rather than inhibition of PB^{131}I levels produced by the iodide load. It therefore seemed logical to study the phenomenon of inhibition of uptake and the variations in behaviour of the iodide concentration mechanism exhibited by differing thyroid conditions at short time intervals after/

after the administration of the iodide load; for it seemed likely that the results obtained would then be due principally to changes in ^{131}I trapping and not to changes in PB^{131}I synthesis or release (7).

Accordingly I elected to study the thyroidal uptake of stable and radioiodine immediately after the administration of 2 mg potassium iodide (KI) and to compare these findings to results of similar studies made on the previous day using the short lived isotope ^{132}I (half life = 2.3 hours) without the addition of KI.

In order to abolish difficulties which might have arisen in interpretation of the results due to variation in the absorption of the iodide load from the bowel over a short period of time the intravenous route was chosen for administration of KI.

MATERIALS

Five patients with simple goitre, 6 patients rendered euthyroid after partial thyroidectomy, 2 patients with Hashimoto's disease and 5 patients rendered euthyroid by ^{131}I therapy for thyrotoxicosis were studied. The mean ages were similar in all the groups studied and all patients were female. The diagnosis of Hashimoto's disease was made on clinical grounds, by the finding of autoantibodies to thyroglobulin by a precipitin technique (8) and to thyroid "microsomes"/

"microsomes" by a complement fixing immunofluorescence technique (9) and also by the demonstration in both patients of butanol insoluble radioiodinated compounds in the serum 48 hours after a 25 uc tracer dose of ^{131}I (10). The patients who had been treated for thyrotoxicosis by ^{131}I and by thyroidectomy were judged to be euthyroid on clinical grounds (11) on the results of ^{131}I studies (12) and by measurement of the stable protein-bound iodine ($PB^{127}I$) (13). In the patients with simple goitre the diagnosis was made on clinical grounds and by the results of ^{131}I studies and of $PB^{127}I$ estimations.

METHODS

A Before KI administration

^{132}I was milked from a ^{132} Tellurium column containing sodium ^{132} Tellurite adsorbed on aluminium oxide gel. The column was supplied by the radiochemical Centre, Amersham. Figs. 1 and 2 show the apparatus which was used to collect and measure the ^{132}I. I made up a sterile solution of N/100 NH_4OH and added 1 ml. of this solution to 1 litre of sterile normal saline. 10 ml. of saline was then allowed to run slowly through the column. ^{132} Tellurium transmutes to ^{132} Iodine by radioactive decay. The ^{132}I which was washed off the column was counted in an ionisation chamber and the amount/

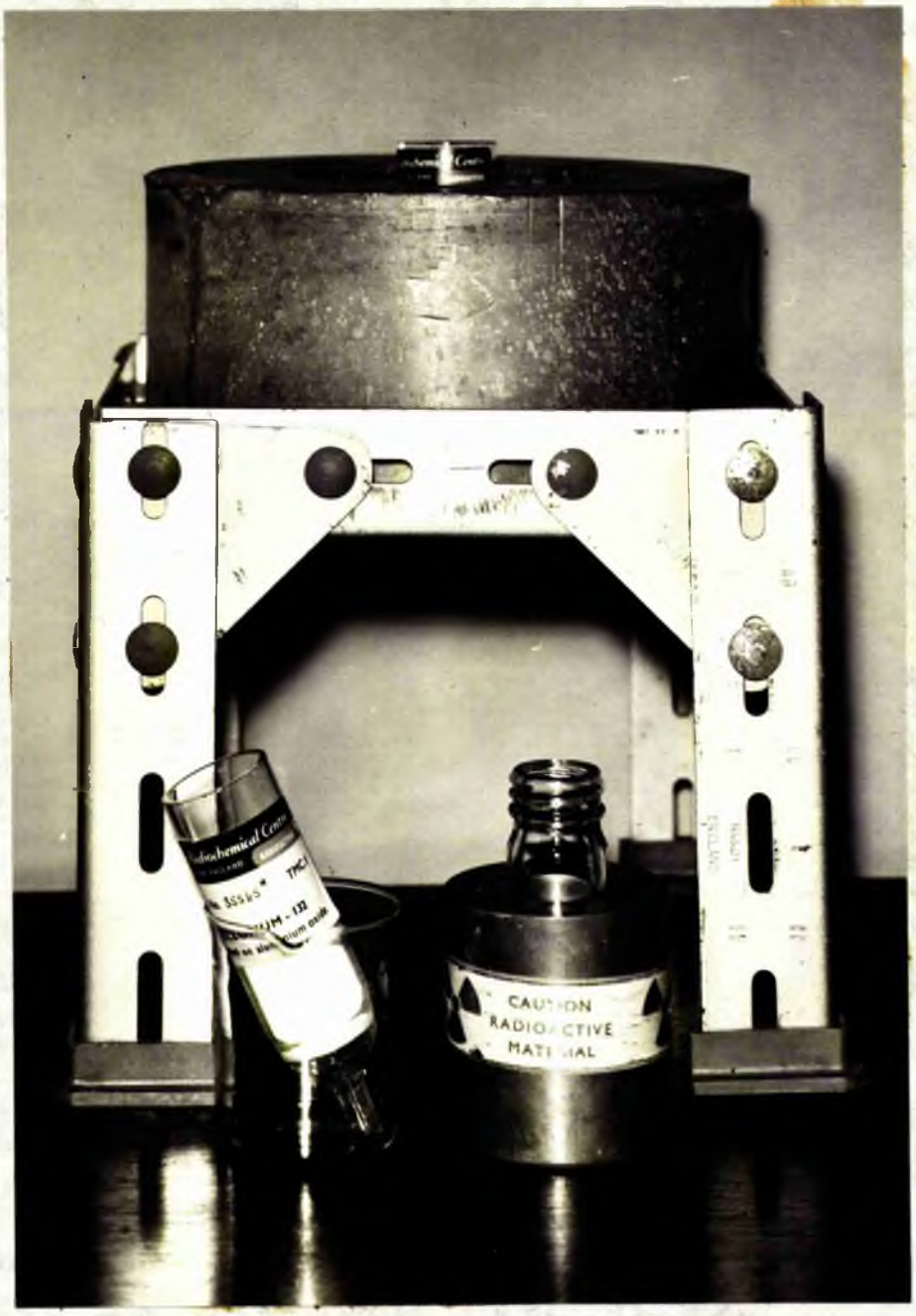

FIGURE 1 The collection of ^{132}I was effected by running 20 ml of extremely dilute NH_4OH through the Tellurium column and collecting the effluent underneath.[4] The figure shows 2 Tellurium columns, one just visible in the lead shielding and one in front of the shielding. The universal container which collected the ^{132}I by being placed underneath the column is also shown. The heavy lead shielding round the column is necessary because ^{132}I has two heavy γ_0 rays of 1.41 and 2.00 MeV respectively.

FIGURE 2 The ionization chamber (left) and DC amplifier which were used to measure the millicurie doses of ^{132}I collected from the ^{132}I Tellurium column. The sample to be measured was placed in a perspex holder so that it was exactly in the centre of the ionization chamber. The current generated in the chamber by the sample was amplified and read on the scale of the amplifier. From this reading the amount of ^{132}I present in the sample was calculated as described in the text.

amount of radiation present was calculated against a standardised ^{60} Cobalt source kindly supplied by the Radiochemical Centre as follows:

If Y uc ^{60}Co give a deflection of M divisions on the ionisation chamber

and X uc ^{132}I give a deflection of D divisions on the ionisation chamber

and K factor for ^{132}I = 11.2

and K factor for ^{60} Co = 13.6

then X uc ^{132}I $= \frac{13.6\ DY}{11.2\ M}$ uc ^{132}I

The ^{132}I was then sterilised in a pressure cooker to prepare it for intravenous injection.

Approximately 25 uc of ^{132}I was administered intravenously and the thyroidal radioiodine plasma clearance rate was measured over the next 30 minutes by the method of Berson et al (14). A minor modification used was that the accumulation of ^{132}I in the thyroid was monitored continuously on a Honeywell Chart Recorder coupled to a ratemeter and the graph was then sampled at 30 second intervals for the next 20 minutes to allow thyroidal clearance to be calculated in the usual manner. The factor 0.83 was used to correct for backscatter of radiation from the vertebral column for experience in over 500 clearances using the Berson technique has shown that this is a valid correction factor.

The/

The plasma inorganic iodine (PII) was measured over the next 90 minutes by a modification of an isotope dilution method which I have designed to be used validly with the Berson technique of estimating thyroidal ^{132}I plasma clearance rate (15). The validation of this technique is described in detail in Part 1 of the thesis and only the details of performance of the method will be presented here.

Precisely 35 minutes after the intravenous injection ^{132}I the bladder was completely emptied and the urine radioactivity was measured as is required by the Berson technique for calculation of ^{132}I clearance rate. Each patient then drank a large (10 fluid ozs.) glass of water to ensure that it would be possible to void urine at 120 minutes. The 120 minute specimen was collected in especially prepared ^{127}I - free glass ware for estimation of radioactivity and ^{127}I. A 5 ml. blood sample was then taken into a heparinised bottle 77 minutes after ^{132}I injection for estimation of plasma radioactivity. One ml. samples of urine and plasma were assayed for radioactivity in a well type scintillation counter. Urine ^{127}I was estimated by the method of Farrell and Richmond (13); analyses of ^{127}I were performed in duplicate on each sample of urine. PII was calculated from the equation.

(1)/

(1) PII (ug/100 ml) = $\frac{\text{Urinary iodine (ug/100 ml) x plasma radioiodine (cpm/100 ml)}}{\text{Urinary radioiodine (cpm/100 ml)}}$

The principles underlying the measurement of PII by isotope dilution techniques are fully discussed earlier (p. 34). Excellent accounts of these principles are given by Stanley (16) who first devised them and by Wayne, Koutras and Alexander (6).

The absolute amount of stable iodine (^{127}I) taken up by the thyroid (AIU) over the half hour period of clearance study was calculated from the formula of Alexander et al (6).

(2) AIU (ug/hr) = Thyroidal plasma ^{132}I clearance rate (ml/min) x PII (ug/100 ml) x 0.6

The factor 0.6 converts ug/100 ml. to ug/ml. and ml/min to ml/hr. Since the AIU was being calculated over the 30 minute interval of clearance study for purposes of comparison with the AIU 30 minutes after intravenous administration of KI, the factor $\frac{0.6}{2}$ rather than 0.6 was used.

B. <u>After KI administration</u>

On the following day 2 mg KI solution was mixed thoroughly with approximately 25 uc ^{131}I and the mixture was injected intravenously. The endogenous PII is now small compared with PII levels consequent on iodide injection (values after iodide injection ranged from 5 to 8 ug/100 ml compared to 0.1 - 0.3 ug/100 ml before injection).

The/

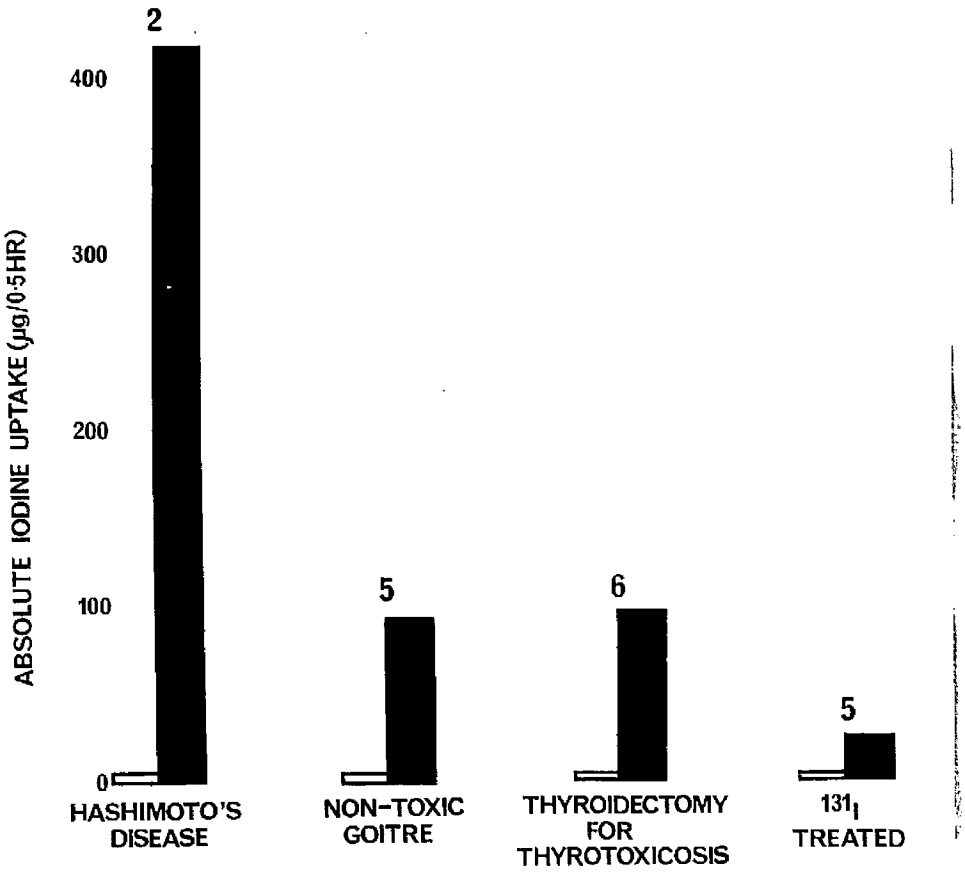

FIGURE 3 The mean absolute uptake of stable iodine by the thyroid calculated over the half hour period from the administration of radioiodine before and after the addition of KI carrier to the tracer dose in various thyroid conditions. The numbers on top of each histogram refer to the numbers of patients in each category. The term non-toxic goitre refers to the patients with simple goitre.

The endogenous PII was therefore neglected and the AIU was calculated from a knowledge of the thyroidal ^{131}I uptake at 30 minutes and the specific activity of the injected radioiodine.

RESULTS

The results are shown in Table 1 (p.326) and in Fig. 3. The mean AIU in the patients with simple goitre rose from 2.63 ± 0.97 (mean ± standard deviation) ug/0.5 hour before the administration of KI to 93 ± 29.8 ug in the half hour immediately following the intravenous administration of KI. In patients with Hashimoto's disease the AIU rose from a control value of 2.22 ug/0.5 hour to 417 ug/0.5 hour. In patients thyroidectomised for thyrotoxicosis a mean rise from 1.14 ± 0.56 ug/0.5 hour to 95 ± 78.2 ug/0.5 hour was observed. The patients who had received ^{131}I therapy for thyrotoxicosis on the other hand demonstrated a relatively poor trapping response to the iodide load: a rise of AIU from 2.12 ± 0.74 ug/0.5 hour to 23 ± 13.7 ug/0.5 hour being observed in these patients. The individual results for each of the 18 patients in this experiment are shown in Appendix A (p.330) which also shows the PII and thyroidal plasma radioiodine clearance values before KI.

These/

These results mean that patients with Hashimoto's disease showed greatest avidity for the KI load in the half hour period immediately following iodide administration followed by the patients who had been thyroidectomised for thyrotoxicosis, patients with simple goitre and patients treated by ^{131}I for thyrotoxicosis. The differences in AIU during this interval are highly significant for patients treated by ^{131}I compared with simple goitre $P < 0.01$) and for patients treated with ^{131}I compared with the patients with Hashimoto's disease ($P < 0.0001$). They are probably also significant for patients treated by thyroidectom y compared with patients treated by radioiodine because all of the former patients have higher AIU's than the latter (Appendix A p.330). Such is the large standard deviation of the observations on the thyroidectomised patients, however that a conventionally accepted statistical difference is not apparent between these two groups. ($0.1 > P < 0.05$).

DISCUSSION

The results of this experiment gave quite unexpected results. The disparity between the AIU 30 minutes after intravenous KI injection was quite striking when the behaviour of patients with Hashimoto's disease, simple goitre and radiation and operation thyroid remnants/

remnants were compared. A close examination of the PII levels, plasma thyroidal ^{132}I clearance rates and AIU values which were obtained on the control day prior to the experiments with KI did not show any obvious differences between the findings in each group which might explain this disparity. I took the patients with simple goitre as my reference point. They had a mean rise in ^{127}I uptake after exposure to the iodide load of 90 ug/0.5 hour (second AIU - first AIU) and did not demonstrate significant iodide inhibition, i.e., did not show depression of ^{131}I uptake at 24 hours. As ^{127}I and ^{131}I are handled in an identical fashion by the thyroid it was not unreasonable to conclude that at 24 hours a fair amount of the iodide dose given in the oral iodide inhibition test was residing in the thyroid gland. The results given by the patients with Hashimoto's disease differed from this. Their mean ^{127}I uptake after exposure to the iodide load rose by 415 ug/0.5 hour, a value much higher than that of the patients with simple goitre: yet 24 hours after KI given orally in the iodide inhibition test showed a marked inhibition of ^{131}I (and presumably also of ^{127}I) uptake. The patients thyroidectomised for thyrotoxicosis behaved somewhat similarly to the patients with Hashimoto's disease. Their mean AIU rose after KI/

KI administration by 94 ug/0.5 hours, a value very similar to that of the patients with simple goitre. In the oral iodide inhibition test however the 24 hour uptake of ^{131}I (and presumably therefore of ^{127}I) of the patients with a thyroidectomy remnant was much less than that of the patients with simple goitre. Only the patients treated by ^{131}I therapy for thyrotoxicosis behaved as one might have expected: they had a very much lower rise in ^{127}I uptake following intravenous KI administration (21 ug/0.5 hour) than the patients with simple goitre and corresponding to this their 24 hour ^{131}I (and presumably ^{127}I) uptake was also very much lower than that of these patients.

It seemed logical that these results could have only one explanation. At some period ranging from 30 minutes to 24 hours after intravenous injection of KI with the tracer dose, some of the ^{127}-^{131}I mixture accumulated in the thyroid gland during the initial study period of 30 minutes must be being discharged.

FURTHER EXPERIMENT

To test this hypothesis I studied the pattern of thyroidal uptake of radioiodine before and after the addition of 2 mg KI solution to the intravenous tracer dose for 30 to 60 minutes following injection by means of/

of a Honeywell Chart Recorder coupled to a ratemeter. Serial counts of thyroid radioactivity were made thereafter for periods up to 6 hours.

I studied 2 patients with Hashimoto's disease, 2 patients thyroidectomised for thyrotoxicosis and 2 patients treated by ^{131}I for thyrotoxicosis. The results of one such observation on a patient with a thyroidectomy remnant are shown in Figure 4. The line joining the open circles refers to the pattern of thyroidal ^{132}I uptake plotted against the square root of time (thyroidal uptake is initially a parabolic function) when the tracer dose was administered intravenously without the addition of KI. The line joining the closed circles outlines the pattern of thyroidal $^{127-131}I$ uptake when 2 mg KI had been added to the ^{131}I tracer dose on the following day. It can be seen that under these circumstances the initial $^{127-131}I$ uptake is followed by spontaneous discharge of radioactivity from the thyroid gland and that this discharge continues for at least 6 hours. To obviate the unlikely possibility that the discharge of radioactivity was due to rapid synthesis and release of labelled hormone as early as 40 minutes after $^{127-131}I$ administration,/

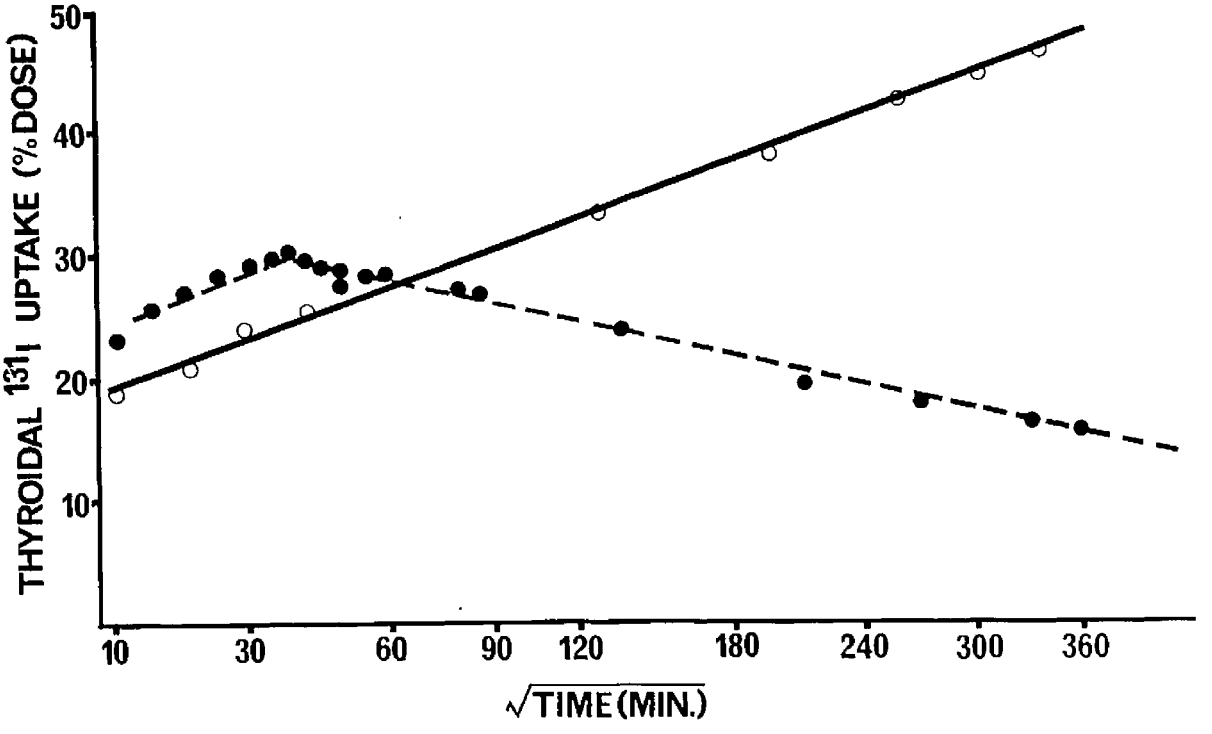

FIGURE 4 Thyroidal radioiodine uptake patterns when the tracer dose of radioiodine is administered intravenously with (black circles) and without (open circles) 2 mg KI to a patient who had undergone thyroidectomy for thyrotoxicosis. When 2 mg KI is added to the tracer, the initial ^{131}I uptake is followed by spontaneous discharge of radioactivity from the thyroid gland. No radiohormone was detected in the plasma during the period 0 - 4 hours following administration suggesting that only ^{131}I was being discharged from the gland.

administration, plasma was checked for radioactivity while the thyroid radioactivity was falling. No plasma radioactivity was demonstrable after passage through an Amberlite IRA 400 (Cl) ion exchange column, a finding which suggests that no radiohormone was present in the plasma.

DISCUSSION

It is possible that the initially rapid uptake and discharge pattern of Fig. 4 is not seen in all patients with Hashimoto's disease nor in all thyroidectomy remnants. I have observed the phenomenon in the two patients with Hashimoto's disease whom I studied but in only one of the two thyroidectomy remnants. It does seem likely that the uptake-discharge phenomenon may account for the iodide inhibition seen in a good proportion of the cases with Hashimoto's disease because Owen and his associates (17) who performed a Berson technique to measure plasma thyroidal ^{131}I clearance rates in 1250 patients found 11 who exhibited a rapid uptake, early discharge phenomenon; 4 of these patients had Hashimoto's disease but none of the four had been given an iodide load. I have shown (Fig. 4) that this discharge is much more likely to occur when the/

the patient is given a 2 mg KI load and yet even without the iodine load the patients studied by Owen et al demonstrated a spontaneous discharge of ^{131}I from the gland.

The findings in the two patients treated by ^{131}I therapy for thyrotoxicosis showed, as one would have expected, that the rate of uptake of $^{127-131}I$ was very slow in both cases and accordingly the inhibition of 24 hour thyroidal $^{131-127}I$ uptake in the iodide inhibition test seen in the ^{131}I treated gland most probably represents a truly decreased functional capacity of the gland to trap iodide.

Neither Feinberg et al (18) nor Paris and his colleagues (19,20) were able to explain the phenomenon of iodide inhibition in the patients they studied, but it seems likely that the uptake-discharge phenomenon which I have described may have been at least partly responsible for the phenomenon of iodide inhbition which was shown by Paris et al (21) to occur in patients with iodide goitre. Table 2(p.328) taken from Paris' findings (19) shows that in 3 patients with iodide goitre the twenty four hour thyroidal ^{131}I uptake was lower than the/

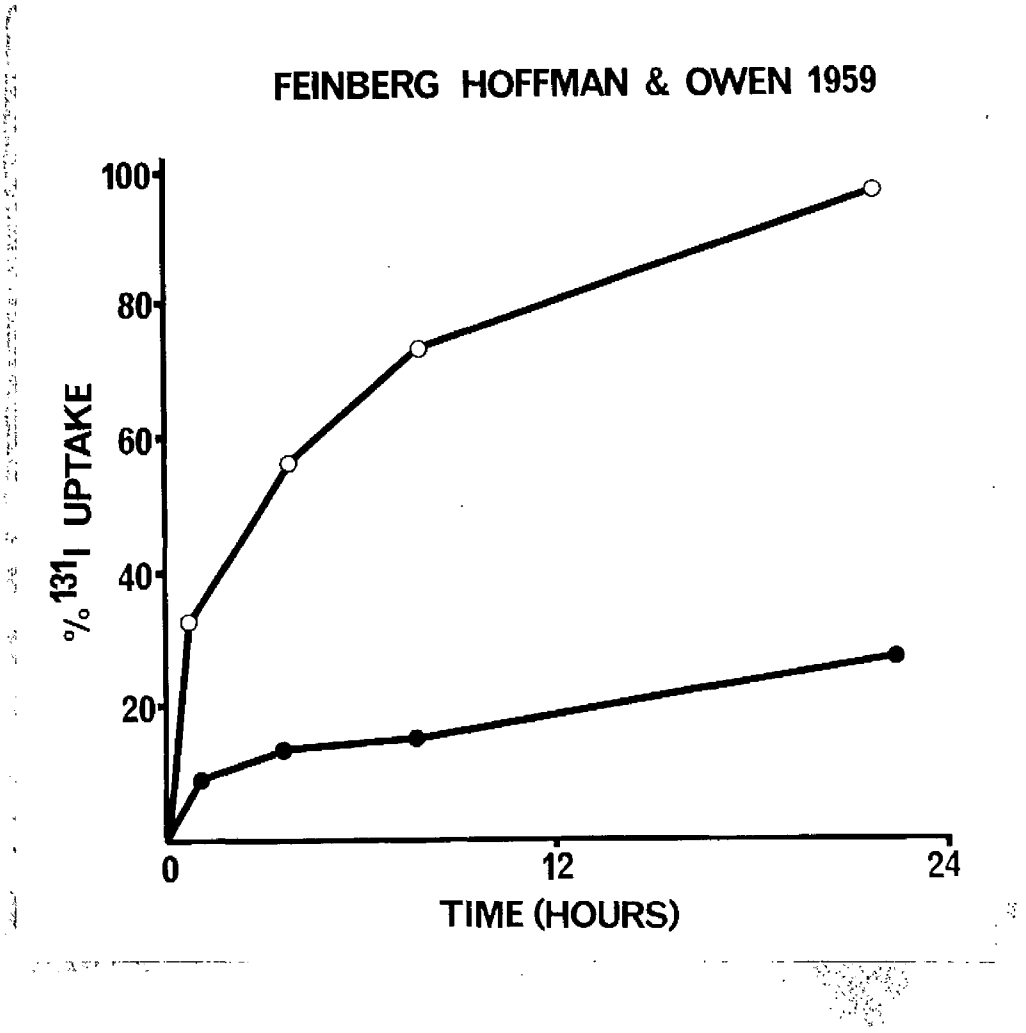

FIGURE 5 Data plotted from the figures of Feinberg et al (1959) J. clin. Endocr. 19, 567. Thyroidal radioiodine uptake patterns when the ^{131}I tracer dose is given orally with (black circles) and without (open circles) 2 mg KI to a thyrotoxic patient. The inhibition of ^{131}I uptake produced by KI which Feinberg et al observed in their patients is seen one hour after the tracer dose has been given.

the 6 hour uptake when 2 mg KI was added to the ^{131}I tracer dose. This finding suggests that $^{127-131}I$ mixture was being discharged from the gland in the period 6 to 24 hours following oral administration of the iodinated tracer dose in much the same way as discharge occurred in my patients from 0 to 6 hours following intravenous administration of the dose. The authors have not commented on this aspect of their results but it seems to me a significant one. Feinberg (18) who showed iodide inhibition in his patients with thyrotoxicosis measured the $^{127-131}I$ uptake patterns of these patients after iodide throughout the day, on the other hand and found that there was a consistently depressed uptake after iodides as is shown in Figure 5. However he did not measure the thyroidal $^{127-131}I$ uptake until 4 hour had elapsed after the oral administration of KI and it may be that he missed a very early rapid uptake-discharge phenomenon in these patients. I cannot comment further on this as I have not demonstrated iodide inhibition in the thyrotoxic patients whom I studied.

Two possible mechanisms for the uptake-discharge phenomenon

The uptake-discharge phenomenon which I have described is very reminiscent of the discharge of ^{131}I which occurs from/

from the thyroid when $KClO_4$ or KSCN is administered to patients who have difficulty in oxidation and subsequent organification of iodide either because of dyshormonogenesis (21-28), Hashimoto's disease (12,29-31), iodide goitre (32,33) or the administration of other drugs known to inhibit the binding of iodide to tyrosine residues within the thyroid gland (34-37). It has been known for many years that one action of iodide itself on the thyroid is to block the oxidation and organification of free intrathyroidal iodide (16,38-42). It is tempting to speculate that iodide is increasing or enhancing a mild underlying defect in iodide organification and that under these circumstances iodide is discharged from the gland. However, $KClO_4$ discharge tests performed on 4 patients with Hashimoto's disease who exhibited iodide inhibition and on one patient who was shown to exhibit the uptake-discharge phenomenon were negative suggesting that they did not have an appreciable defect in iodide binding. It may be that these patients did have a slight impairment in binding power insufficiently great to be revealed by the $KClO_4$ test but which was enhanced by the iodide load. A further point however against this concept is the fact that the patient with Pendred's syndrome which is known to be associated with defective organic binding of iodide (20-27)/

(20-27) did not demonstrate significant iodide inhibition (32 per cent) although he discharged 35 per cent of the accumulated thyroidal ^{131}I in the $KClO_4$ discharge test, (upper limit of normal 12 per cent (12)), a finding which suggests he did have an appreciable defect in iodide organification. This patient, however, had been receiving thyroxine therapy for 2 years prior to the performance of the iodide inhibition test and this may invalidate the results of it.

To my knowledge defective organification of iodide has not been demonstrated in the thyroidectomy remnant and it may be that the uptake-discharge phenomenon may arise in these patients in a different fashion. Stewart (42) has shown that thyroidal inorganic iodide accumulated in the thyroids of patients with simple goitre in the performance of the iodide inhibition test may be discharged by $KClO_4$. This finding has been confirmed (43) and it suggests that in these glands the relative capacity to trap excess iodide has outstripped the capacity to bind excess iodide in organic form. The iodide lies free in the gland and can be discharged by $KClO_4$. It is probable that much the same thing happens in the thyroidectomy remnant except that the intra-thyroidal storage pool for iodide is very much less than in patients with simple goitre because it has been physically/

physically reduced by operation. Under these conditions the active thyroidectomy remnant which is known to trap and turn over ^{131}I at a fast rate (44) may initially accumulate much more of the KI load in the iodide inhibition test than it can accommodate and early $^{127-131}I$ discharge then occurs. It is equally likely that a reduced intrathyroidal iodine storage pool is partly responsible for the $^{127-131}I$ discharge in Hashimoto's disease. A high turnover rate of ^{131}I due to a small intrathyroidal iodine pool has been suggested in patients with Hashimoto's disease (12,30,45-46) and Buchanan et al (31) who measured the intrathyroidal exchangeable iodine pool in 11 patients with Hashimoto's disease found it to be markedly reduced in almost all of them.

None of these speculations are likely to be relevant to the radiation remnant where the reason for the response to the iodide inhibition test would seem to lie in a failure of reserve trapping capacity of the thyroid to accumulate the increased plasma iodide load presented to it. Support for this concept is provided by the study of Eckert et al (44) who came to somewhat similar conclusions from different observations. In a study of the ^{131}I treated remnant they showed that the ability/

ability of the gland to expand the iodide trapping mechanism following Carbimazole administration was reduced.

The next section of this part of the thesis describes some experiments which for the sake of completeness I undertook to try to find out why the radiation remnant cannot trap excess iodide.

SUMMARY

Studies of ^{131}I kinetics and of stable iodine metabolism before and after the intravenous administration of 2 mg KI to 2 patients with Hashimoto's disease, 6 patients with a thyroidectomy remnant, 5 patients who had received ^{131}I therapy for thyrotoxicosis and 5 patients with simple goitre were undertaken in an attempt to explain the phenomenon of iodide inhibition. These studies suggested that there are 2 possible mechanisms of occurrence of the phenomenon. One mechanism which occured in patients with Hashimoto's disease and in patients with a thyroidectomy remnant consisted of an initially rapid uptake of $^{127-131}I$ mixture by the thyroid followed by a prompt discharge of $^{127-131}I$ from the gland. The second mechanism, seen in patients treated by ^{131}I therapy for thyrotoxicosis seemed to be due to a truly decreased functional capacity of the glands of these patients to trap iodide. Possible reasons which might underlie the first of these mechanisms were discussed.

REFERENCES

1. Riggs, D.S. (1952),
Pharmacol. Rev. 4, 284.

2. Alexander, W.D., Koutras, D.A., Crooks, J.,
Buchanan, W.W., Macdonald, E.M., Richmond, M.J.
and Wayne, E.J. (1962),
Quart. J. Med. NS 31, 281.

3. Koutras, D.A., Alexander, W.D., Buchanan, W.W.,
Crooks, J. and Wayne, E.J. (1960),
Lancet, 2, 784.

4. Koutras, D.A., Alexander, W.D., Buchanan, W.W.,
Crooks, J. and Wayne, E.J. (1960),
Scot. med. J. 5, 331.

5. Koutras, D.A., Alexander, W.D., Buchanan, W.W.,
Crooks, J. and Wayne, E.J. (1961),
Acta. Endocr. 37, 597.

6. Wayne, E.J., Koutras, D.A. and Alexander, W.D.,
Clinical Aspects of Iodine Metabolism, Blackwell
Scientific Publications, Oxford (1964), p.7ff.

7. Soderberg, U. (1958),
Acta Phys. Scand. Suppl. 42, 147.

8. Anderson, J.R., Buchanan, W.W., Goudie, R.B. and
Gray, K.G. (1962),
J. clin. Path. 15, 462.

9. Buchanan, W.W., Crooks, J., Alexander, W.D., Bruce, W.,
Anderson, J.R., Goudie, R.B. and Gray, K.G. (1962),
J. Endocr. 24, 115.

10. Owen, C.A. Jr., and McConahey, W.M. (1956),
J. clin. Endocr. 16, 1570.

11. Wayne, E.J. (1960),
Brit. med. J. 1, 1 and 78.

12. Murray, I.P.C. and McGirr, E.M. (1960),
Brit. med. J. 1, 838.

13. Farrell, L.P. and Richmond, M.H. (1961),
Clin. Chim. Acta. 6,620.

14. Berson, S.A., Yalow, R.S., Sorrentino, J. and Roswit, B.
(1952),
J. clin. Invest. 31, 141.

15. Boyle, J.A., Sloss, A.E., Macdonald, E.M. and Gray, M., (1965), J. clin. Endocr. 25, 1035.

16. Stanley, M.M. (1949), J. clin. Endocr. 9, 941.

17. Owen, C.A., Jr., McCants, R.S. and McConahey, W.M., (1960), J. clin. Invest. 39, 790.

18. Weinberg, W.D., Hoffman, D.L. and Owen, C.A. (1959), J. clin. Endocr. 19, 567.

19. Paris, J., McConahey, W.M., Owen, C.A., Woolner, L.B. and Bahn, R.C. (1960), J. clin. Endocr. 10, 57.

20. Paris, J., McConahey, W.M., Taurxe, W.N., Woolner, L.B. and Bahn, R.C. (1961), J. clin. Endocr. 21, 1037.

21. Stanbury, J.B. and Hedge, A.N. (1950), J. clin. Endocr. 10, 1471.

22. Clayton, A.W., Smith, J.D. and Leiser, A. (1958), J. Pediat. 52, 129.

23. Morgans, M.E. and Trotter, W.R. (1958), Lancet, 1, 607.

24. McGirr, E.M., Hutchison, J.H. and Clement, W.E., (1959), Scot. med. J. 4, 107.

25. McGirr, E.M. in Clinical Endocrinology I, Grune and Stratton Inc. New York, 1960, p.133.

26. Fraser, C.R., Morgans, M.E. and Trotter, W.R. (1960), Quart. J. Med. 29, 279.

27. Trotter, W.R. (1960), Postgrad. Med. J. 36, 425.

28./

28. Parker, R.M. and Beierwaltes, W.H. (1961),
J. clin. Endocr. 21, 21.

29. Morgans, M.E. and Trotter, W.R. (1957),
Lancet, 1, 553.

30. Doniach, D. and Hudson, R.V. (1957),
Brit. med. J. 1, 672.

31. Buchanan, W.W., Koutras, D.A., Alexander, W.D.,
Crooks, J., Richmond, M.H., Macdonald, E.M. and
Wayne, E.J. (1961),
J. clin. Endocr. 21, 806.

32. Paley, K.R., Sobel, E.S. and Yalow, R.S. (1958),
J. clin. Endocr. 18, 79.

33. Begg, T.B. and Hall, R. (1960),
Quart. J. Med. NS 32, 351.

34. Stanley, M.M. and Astwood, E.B. (9948),
Endocrinology, 42, 107.

35. Edwards, D.A.W., Rowlands, E.N. and Trotter, W.R. (1954),
Lancet, 2, 1051.

36. Morgans, M.E. and Trotter, W.R. (1955),
Lancet, 2, 164.

37. Trotter, W.R. (1957),
Postgrad. med. J. 33, 338.

38. Morton, M.E., Chaikoff, I.L. and Rosenfeld, S. (1944),
J. biol. Chem. 154, 381.

39. Wolff, J. and Chaikoff, I.L. (1948),
J. biol. Chem. 174, 555.

40. Wolff, J., Chaikoff, I.L., Goldberg, R.C. and Meier, J.R.
(1949),
Endocrinology, 45, 504.

41. Braverman, L.E. and Ingbar, S.H. (1963),
J. clin. Invest. 42, 1216.

42. Stewart, R.D.H.,
Prince of Wales Hospital, Randwick, NSW, Australia, (1965),
Personal Communication at Symposium on Balance and
Dynamics of Iodine in Iodine Deficiency States and Endemic
Goitre, Brussels, Belgium.

43./

43. Boyle, J.A.,
Unpublished observations.

44. Eckert, H., Green, M., Kilpatrick, R., and Wilson, C.M. (1960),
Clin. Sci. 20,80.

45. Macgregor, A.G. and Wayne, E.J. in
Modern Trends in Endocrinology, Ed. H. Gardiner-Hill, Butterworth & Co. Ltd., London, (1958), p.34.

46. Owen, C.A. Jr., in
Diagnostic Radioisotopes, Blackwell Scientific Publications, Oxford, (1959), p.56.

PART 2

SECTION 3

STUDIES OF THE MECHANISM OF OCCURRENCE OF IODINE INHIBITION (CONTINUED)

In the previous section of this part of the thesis I have presented evidence which suggests that the mechanism of iodide inhibition in patients rendered euthyroid by ^{131}I therapy consists of a truly decreased functional capacity of the thyroid gland to trap iodide. For the sake of completeness in detailing my work on the phenomenon of iodide inhibition I shall briefly describe experiments which I undertook to try to find out why these glands could not trap the excess iodide in the iodide inhibition test. There were two possible reasons for this inability. The first was that there was some abnormality of the thyrotoxic thyroid gland with regard to iodide trapping and that this abnormality was enhanced by the effect of ^{131}I radiation. As I had not demonstrated iodide inhibition in frankly thyrotoxic subjects in the initial study, this line of enquiry did not seem a particularly fruitful one to pursue.

The second possibility, which seemed more promising, as it was susceptible of experimental study, was that the decreased functional capacity to trap iodide had been directly produced by the effect of ^{131}I radiation on these thyrotoxic glands. If this were the case it might be possible to show that radiation injury impaired the functional capacity of normal thyroid glands to trap iodide.

I decided to approach the problem in two separate ways: by/

by studying the phenomenon of iodide inhibition in patients whose thyroid glands were unavoidably included in the treatment volume during radical x-ray therapy for early cancer of the larynx, and also by a series of animal experiments in which the capacity of the rat thyroid gland to trap organic iodide was studied while the thyroid was subjected to increasing radiation injury by ^{131}I. The study with the patients is described first.

MATERIALS

Ten patients whose presumably normal thyroid had been heavily (and unavoidably) irradiated during radical x-ray therapy for early cancer of the larynx were selected for study. Table 1(p.334) shows their sex and the ages at which treatment was commenced. Only two were female patients because laryngeal cancer is predominantly a disease of the male (1). Table 1 also shows the total doses of radiation in rads (fractionated over a treatment time of 3 to 4 weeks) and the interval in years between treatment and the time of study. All patients were ambulant and the laryngeal cancer was either cured or controlled.

METHODS

In all patients thyroid function was assessed by clinical interview and examination (2) and by routine radioiodine tests of thyroid function (3). The serum $PB^{127}I$ concentration was measured in all of them (4) and their sera were examined for the presence of anti-thyroglobulin autoantibody by the tanned red cell haemagglutination test (5) and for complement fixing antibody to thyroid "microsomal" antigen using a fluorescent antibody technique (6). The iodide inhibition test was performed using the standard 2 mg. potassium iodide (KI) dose as described in the first section of this part of the thesis.

RESULTS

Table 1 (p. 384) shows the results obtained for 24 hour thyroidal ^{131}I uptake before and after the KI load together with the calculated percentage iodide inhibition for individual patients. The results of serum PB^{127}I estimations are also included in this table.

None of the patients were thought to be clinically hypothyroid and the serum PB^{127}I level was in all of them above the accepted lower limit of normal (3.5 ug per cent) in our laboratory. The normal accepted lower limit of normal for the thyroidal ^{131}I uptake at 24 hours in our radioisotope laboratory is 20 per cent of ^{131}I dose and in only one patient was the uptake less than this (19 per cent). In this patient however the PB^{127}I was 6.0 ug per cent and she was thought clinically to be euthyroid. The PB^{131}I at 48 hours was negligible in all cases. In none of these patients could antithyroid antibodies be detected.

The results of the iodide inhibition test were similar to those obtained in the control group. In no patient in this study was a percentage inhibition greater than 55 per cent seen and the mean inhibition of 34 per cent is not significantly different from the 25 per cent of the control group ($P > 0.10$).

DISCUSSION

The results of this study showed that X-irradiation given as fractionated doses over three to four weeks in totals of from 5000 to 6000 rads (mean 5805 rads) did not impair the long term function of the non-toxic human thyroid gland (from 2 to 5.5 years later) as judged by clinical examination, radioiodine study and serum PB^{127}I measurements. These observations are in accord with the findings of other workers (7).

By contrast, ^{131}I irradiation given in doses of 5000 to 10,000 rads in the treatment of thyrotoxicosis is followed by a high incidence of late onset hypothyroidism (8-13) 40 to 50 per cent of cases so treated developing permanent myxoedema. In addition I had shown that the vast majority of patients treated by ^{131}I therapy for thyrotoxicosis have a diminished functional capacity to trap excess iodide when this is presented to their thyroid glands. Normal thyroids however treated in this study with equivalent rad doses of x-rays at equivalent time intervals before examination did not have a diminished reserve capacity to trap the iodide presented in the iodide inhibition test.

These findings could have been done to one of two explanations. Firstly, thyroid irradiation during the course/

course of ^{131}I therapy for thyrotoxicosis might not have impaired the reserve trapping capacity of the thyroid cells, this impairment being due to some other factor; or secondly thyroid irradiation might indeed have produced impairment of the reserve trapping capacity but because thyrotoxic thyroid cells were inherently more radio sensitive than normal thyroid cells iodide inhibition was not demonstrated in the normal radioresistant cells. It is known that increased cell metabolism and oxygenation, both features of the thyrotoxic gland, sensitise a wide variety of mammalian cells to radiation injury (14-16) and from a study of the rad doses required to render euthyroid patients undergoing ^{131}I treatment for angina pectoris hypothyroid, it has been concluded that the normal thyroid is indeed more radioresistant than the thyrotoxic thyroid (17). Studies of the action of ^{131}I in patients with thyroid cancer have led to similar conclusions (18).

I reasoned that if the second explanation were true, I might have to give very large radiation doses to normal patients if I wished to demonstrate iodide inhibition in the irradiated normal gland and so prove that the phenomenon was a hallmark of thyroid cell radiation injury. It was not possible for me to obtain cardiac patients treated for angina pectoris by ^{131}I and therefore I decided to use the rat thyroid gland as a model for study of this point.

Initial Experiment/

Initial Experiment

A preliminary experiment was necessary to determine the dosage of iodide required to inhibit the ^{131}I uptake of the normal non-irradiated rat thyroid gland so that the correct dose of iodide (corresponding to 2 mg KI in the human) could be given in subsequent studies. Table 2 (P. 337) shows the results of an experiment where 0,1,4,10,20,40 and 80 ug of ^{127}I were injected with 0.5 uc ^{131}I into adult female Wistar rats (body weight 180 - 250 G.) who had been receiving a standard laboratory diet for 2 weeks prior to study. The animals were killed 24 hours later, the thyroids dissected out and allowed to stand overnight in 5 ml. of 3N NaOh. This procedure caused disintegration of all thyroid tissue. Thyroidal radioactivity was then measured in a Nuclear Chicago automatic scintillation counter and expressed as a percentage of the administered dose. It can be seen that 10 µg ^{127}I given with the tracer dose caused a slight (13 per cent) depression of 24 hour thyroidal ^{131}I uptake from the control value. Twenty ug ^{127}I caused a greater (30 per cent) depression, 40 ug ^{127}I a marked reduction (69 per cent) and 80 µg a profound depression in the ^{131}I uptake. I decided therefore to use doses of 10, 20 and 40 µg ^{127}I to study the functional reserve capacity of/

of the irradiated rat thyroid gland to trap excess amounts of ^{127}I.

I then had to decide how much ^{131}I should be given to the rats if I was to produce radiation injury of the same order as that sustained by thyrotoxic patients during ^{131}I therapy. Maloof (21) has shown that rats given 50 μc ^{131}I exhibit obvious functional and histological changes in the thyroid gland 40 days after administration of the isotope. I decided therefore to use this dose and also a 75 μc dose of ^{131}I for it seemed that these doses would inflict irradiation damage on the rat thyroid.

Materials

Seventy young adult female Wistar rats from the same breeding colony weighing 180-250 g. and reared under standard laboratory conditions were studied. The rats were randomly divided into 10 groups, 5 animals to each group. They were individually marked, weighed in grams and received thyroid irradiation by the intraperitoneal injection of ^{131}I. The plan of this experiment is shown in Table 3 (p.339) where it can be seen that 20 animals received no ^{131}I, 25 received 50 uc ^{131}I (5 of these animals being used later to provide a measure of background radioactivity in the thyroid gland) and 25 received 75 uc ^{131}I, 5 of these also being used later to measure background radiation. The rats were maintained thereafter on normal diet under standard laboratory conditions for 3 weeks. Each animal then received an intraperitoneal injection of 0.5 uc ^{131}I apart from the 10 rats already referred to who were used to provide a measure of thyroid radioactivity prior to the injection of the ^{131}I tracer dose. Zero, 10, 20 and 40 ug doses of ^{127}I were administrated with the ^{131}I tracer dose to groups of the animals who had received 0, 50 and 75 uc ^{131}I, 5 animals in each group (Table 3p.339). The rats who were used for background counting did not receive/

receive ^{127}I. All animals were killed by coal gas 24 hours later, the glands were dissected free and the ^{131}I content was determined as previously described. The percentage uptake was then derived by comparison with a standard.

Results

The results of this experiment are shown in Tables 4 and 5 (p. 341 - 3) where the mean 24 hour ^{131}I thyroidal uptakes and mean percentage inhibition of uptake after allowance for background radioactivity due to the 50 and 75 ng ^{131}I doses, are shown. Appendix A shows the individual counts obtained for each animal prior to the correction for background radioactivity. (see p.345)

A The non-irradiated control group

The non-irradiated control animals who were given the ^{131}I tracer dose without ^{127}I had a mean uptake of 32 per cent. This contrasts with the value of 26 per cent found in the non-irradiated animals given 10 ug ^{127}I with the ^{131}I (an inhibition of 19 per cent of the uptake of the control group) and with the uptakes of 7 per cent and 3 per cent in the groups who received 20 and 40 ug ^{127}I (78 and 92 per cent inhibition respectively).

B The group given 50 ng ^{131}I by intraperitoneal injection

The animals who received 50 ng ^{131}I and no iodide with the ^{131}I tracer had a mean uptake of 22 per cent. This is a significantly lower uptake than that of the non-irradiated control group ($P < 0.05$). The mean uptake of the rats given 50 ng ^{131}I who were studied with the addition of 10 ug ^{127}I to the tracer was 16 per cent and the/

the percentage inhibition of uptake was 29 per cent. This is not significantly different from the 19 per cent inhibition of uptake which was found in the non-irradiated group. The inhibition of uptake produced by addition of 20 and 40 ug ^{127}I to the control group was so great (78 per cent and 92 per cent respectively) that it was not possible to expect further significant differences between these values and the values for irradiated animals.

C. <u>The group given 75 uc by intraperitoneal injection</u>

The rats who received 75 uc ^{131}I had more radiation induced damage in their thyroid glands than did the group treated with 50 uc ^{131}I for they showed a marked inhibition of ^{131}I uptake. The ^{131}I uptake for this group when no carrier iodide was given with the tracer dose was 15 per cent. This value is significantly lower than that of the non-irradiated rats ($P < 0.02$). After 10 ug ^{127}I was given with the tracer dose the ^{131}I uptake was 5 per cent which represents an inhibition of 67 per cent of the original uptake of this group, and is significantly different from the percentage inhibition of the control group ($P < 0.02$). The inhibition of uptake produced by 20 and 40 ug ^{127}I in the control group was so great that it was not possible to show a significantly increased inhibition of uptake in the groups treated with 75 uc ^{131}I who were given iodide loads of this magnitude.

Discussion

Irradiation with 50 and 75 uc ^{131}I which may be calculated to deliver very approximately rad doses of the order of 20,000 and 30,000 rads (19) doses which are in excess of those used to treat hyperthyroidism (20), produces irradiation injury to function (iodide trapping) in the normal rat thyroid (21). This is demonstrated in the present experiment both by the impaired ^{131}I uptake of the residual thyroid mass following irradiation and by the impaired capacity to deal with the 10 ug iodide load (in the 75 uc treated group).

To exclude the possibility that there was an early uptake - rapid discharge phenomenon such as I have described in some patients with Hashimoto's disease, I studied the ^{131}I uptake patterns of heavily irradiated rats in another experiment at 6,12,18 and 24 hours after administration of the ^{127} - ^{131}I mixture. I shall not present details of this study but the results showed that the early uptake - rapid discharge phenomenon did not occur in these rat glands.

These findings suggest that when irradiation injury in the gland is such as to impair the function of the tissue a situation which obtains in the treated patient, significant/

significant iodide inhibition may also be demonstrated particularly when the radiation injury is severe. If it is possible to extrapolate from the rat thyroid to the human gland, which one can do only with extreme caution it would therefore appear that iodide inhibition in patients treated by ^{131}I therapy for thyrotoxicosis may be a reflection of the known irradiation induced morphological and functional disorganization which has been demonstrated by histological and in vivo studies of these glands (20-24). These results do not exclude entirely the possibility that other factors such as a diminished size of the intrathyroidal iodide storage pool may also be important in producing the phenomenon of iodide inhibition in some ^{131}I treated patients.

Many studies have demonstrated that there are two grades of irradiation injury when mammalian cells are exposed to radiation: initially the cells lose their capacity to divide and multiply following moderate irradiation (14,16,25) and then as the rad dose is increased the function of the cells becomes impaired (16,26 - 8). That this general rule is also true for rat thyroid cells has been shown by many workers (29 - 33). In addition Al-Hindawi and Wilson (34) believe that the ^{131}I radiation remnant in the human thyroid would exhibit both grades of irradiation damage if it were possible to measure inhibition of mitosis and cell turnover rates in the/

the thyroid of man.

The animal experiments suggest that there may be a third grade of irradiation injury in the thyroid which supervenes before total failure of cell function: namely, inability to trap the excess iodide load presented with the ^{131}I tracer. Irradiation injury produced by 50 uc ^{131}I was severe enough to cause the second grade of damage to the rats' thyroid cells for they showed impairment of ^{131}I uptake. However the reserve capacity of these cells to trap the same proportion of the excess iodide load (10 ug) remained similar to the control non-irradiated cells. When the irradiation damage was increased however by administering 75 uc ^{131}I doses, the reserve capacity to trap excess iodide also became severely impaired. These findings and the findings of others suggest three grades of irradiation injury occurring with increasing severity of irradiation damage. In the first grade, the capacity of the thyroid cells to multiply becomes impaired. Secondly the function of the gland as a whole becomes impaired due to death of cells which have attempted to multiply. The remaining cells have however the capacity to trap excess iodide presented to them. The third grade occurs when the remaining cells exhibit impaired reserve functional capacity to trap excess iodide.

I hypothesise that these observations might be relevent to the patients treated by ^{131}I therapy who possibly have at least/

least two of these grades of irradiation injury in their glands. Histological studies have shown defective cell reproduction in the ^{131}I treated remnant and it is likely that many microscopically normal looking cells have been sterilised by irradiation (20). Functional abnormalities have been also demonstrated in the post radiation thyroid remnant (22,24,35,36). I have shown in addition that all of these patients once euthyroid demonstrated iodide inhibition and in this respect they may be similar to the rats who received 75 uc who also demonstrated inability to trap an excess iodide load. This suggests a defect in the patients glands similar to that found following severe radiation injury to the rat thyroid gland as both demonstrate the third grade of irradiation injury.

This argument suggests that the irradiation injury in the glands of the patients who have received sufficient ^{131}I to render them euthyroid is likely to be severe and this concept is wholly compatible with the observations of a high rate of thyroid cell failure leading to myxoedema following ^{131}I therapy for thyrotoxicosis in these patients.

SUMMARY

This section of the thesis describes some studies which were undertaken to explain the phenomenon of iodide inhibition which was shown in Section 2 to occur in patients treated with ^{131}I therapy for thyrotoxicosis. It was felt that the most obvious explanation for the failure of these patients' glands to trap the excess iodide presented to them in the iodide inhibition test was that the radiation injury produced by ^{131}I had rendered the thyroid cell abnormal in respect of its reserve capacity to accumulate iodide. This question was approached in two ways. Firstly a study was made of patients who had had the thyroid gland unavoidably included in the treatment volume during radical x-ray therapy for carcinoma of the larynx. I found that these patients did not exhibit the phenomenon of iodide inhibiton. If they had exhibited the phenomenon it would have been strong evidence that radiation injury in ^{131}I treated patients was at least in part responsible for iodide inhibition. A negative finding however did not disprove the hypothesis; the possibility existed that the thyroid gland of a thyrotoxic patient was much more sensitive to irradiation than the normal thyroid gland and there was evidence to support this concept. It therefore appeared that if I was to produce/

produce the phenomenon of iodide inhibition in a normal thyroid gland by radiation injury I should have to employ very large doses of radiation.

As this was not possible in patients I used the rat thyroid gland to pursue the hypothesis that radiation injury was responsible for the phenomenon of iodide inhibition. Initial experiment enabled me first to find the dose range of stable iodide, corresponding to the 2 mg KI dose in man, which should be administered with the ^{131}I tracer dose. I was then able to show that rats given 75 uc ^{131}I 3 weeks prior to study showed a striking inhibition of ^{131}I uptake when 10 ug ^{127}I was administered with the tracer compared with non-irradiated control rats. This inhibition of uptake was not observed in rats who had received a slightly less, though still considerable amount of ^{131}I (50 uc). The findings suggested that my original hypothesis that ^{131}I irradiation injury was responsible for the iodide inhibition seen in patients treated by ^{131}I for thyrotoxicosis, was correct. The phenomenon was not a good index of radiation damage in the rat thyroid gland because it was not observed until disturbances of more obvious parameters of thyroid function, such as iodide trapping, were present.

REFERENCES

1. Willis, R.A. (1960),
Pathology of Tumours, 3rd Ed. Butterworth, London p.303.

2. Wayne, E.J. (1960),
Brit. med. J. 1, 78.

3. Murray, I.P.C. and McGirr, E.M. (1960),
Brit. med. J. 1, 838.

4. Farrell, L.P. and Richmond, M.H. (1961),
Clin. chim. Acta., 6, 620.

5. Anderson, J.R., Buchanan, W.W., Goudie, R.B. and Gray, K.G. (1962),
J. clin. Path. 15, 462.

6. Buchanan, W.W., Crooks, J., Alexander, W.D., Brass, W. Anderson, J.R., Goudie, R.B. and Gray, K.G. (1962),
J. Endocr. 24, 115.

7. Koulumies, M., Voutilainen, A. and Koulumies, R. (1964),
Ann. Med. Int. Fenniae, 53, 89.

8. Beling, U. and Einhorn, J. (1961).
Acta. Radiol (Stockholm), 56, 275.

9. Dunn, J.T. and Chapman, E.M. (1964),
New Eng. J. Med. 271, 1037.

10. Green, M. and Wilson, G.M. (1964),
Brit. med. J. 1, 1005.

11. McGirr, E.M., Thomson, J.A. and Murray, I.P.C. (1964),
Scot. med. J. 9, 505.

12. Macgregor, A.G. in The Thyroid and its Diseases.
ed. A.S. Mason, Pitman Publishing Co. Ltd., London, 1963
p.19.

13. Editorial (1965), Lancet 1, 637.

14. Alper, T. (1960),
Ann. Rev. Nucl. Sci., 10, 489.

15./

15. Gray, L.H. in Lectures on the Scientific Basis of Medicine, Athlone Press, London, 1957-8, p.314.

16. Hewitt, H.B.(1962,) in Lectures on the Scientific Basis of Medicine, Athlone Press, London, p.306.

17. Strong, J.A. and Turner, R.W.D. (1962), Quart. J. Med. 31, 221.

18. Goolden, A.W.G. and Davey, J.B. (1963), Brit. J. Radiol. 36, 340.

19. Hine, G.J. and Brownell, G.L. Radiation Dosimetry, Academic Press, New York, 1956 p. 160

20. Curran, R.C. Eckert, C.H. and Wilson, G.M. (1958), J. Path. Bact. 76, 541.

21. Maloof, F., Dobyns, B.M. and Vickery, A.L. (1952), Endocrinology, 50, 612.

22. Dobyns, B.M. and Didschenko, I, (1961), J. clin. Endocr. 21, 699.

23. Binopoulos, D.E., Kostamis, E.P., Koutras, D.A. and Sfontouris, J. (1962), J. clin. Endocr. 26, 49.

24. Einhorn, J. and Hastad, K. (1961), J. clin. Endocr. 21, 1483.

25. Munro, J.R. (1959), Exp. Cell Res., 18, 76.

26. Puck, T.T. (1960), Progr. Biophys. 10, 237.

27. Lajtha, L.G. and Oliver, R., (1961), Brit. J. Radiol., 34, 352.

28. Baeq, Z.M. and Alexander, P.(1962) in Fundamentals of Radiobiology, Pergamon Press, London. p. 305.

29. Skanse, B.N., (1948), J. clin. Endocr. 8, 707.

30./

30. Crooks, J., Greig, W.R., Macgregor, A.G. and Neinbach, J.A.R. (1964).
Brit. J. Radiol. 37, 300.

31. Dobyns, B.M., Vickery, A.L., Maloof, F. and Chapman, E.M. (1953).
J. clin. Endocr. 13, 549.

32. Potter, G.D., Ramos, A. and Chaikoff, F. (1956).
Endocrinology, 12, 56.

33. Reinach, I. (1956).
Brit. Med. Bull. 14, 10.

34. Al-Hindawi, A.L. and Wilson, G.M. (1965).
Clin. Sci. 28, 555.

35. Werner, S.C. (1956).
J. clin. Invest. 35, 57.

36. Eckert, H., Green, H., Kilpatrick, R. and Wilson, G.M. (1960).
Clin. Sci. 20, 67.

PART 3

CONSTRUCTION OF A MODEL FOR COMPUTER-ASSISTED DIAGNOSIS: APPLICATION TO THE DIFFERENTIAL DIAGNOSIS OF NON-TOXIC GOITRE

The art of diagnosis requires on the one hand the taking of a careful history, the accurate recording of physical signs, the performance of laboratory studies in certain cases, and on the other an interpretation of the information thus provided.

This interpretation requires the clinician's assessment of the probability of the features under consideration occurring in a particular disease. Such an assessment is made in the light of his past experience of the incidence of these features in this and in other diseases. In practice this is often accomplished without difficulty but errors may occur; for even experienced observers may sometimes find it difficult to decide the relative importance which should be attached to different findings. Not only may clinicians attach differing degrees of significance to the same features but a single clinician may also vary in his interpretation on different occasions. Moreover, one particular finding may distract the observer's attention from the consideration of the complete clinical picture.

Ledley and Lusted (1,2) have suggested that statistical techniques might advantageously be applied in the making of a diagnosis, and Wayne and his colleagues (3), using a technique based on discriminant analysis, have widely explored the practical/

practical possibilities of the application of statistical techniques to the diagnosis of clinical problems.

More recently the feasibility of using probability techniques for arriving at a diagnosis has been explored by several authors (4 - 11). As these methods involve calculation of diagnosis from complex equations and from large masses of data, automatic computation using a computer becomes mandatory (10). As Spencer and Vallbona (12) have recently commented "a climate of expectation has developed, the general feeling being that practicality in these usages is just around the corner". Notwithstanding the initial practical studies which have been undertaken in automatic computation of diagnosis using probability theory, however, the accuracy of a computed diagnosis has yet to be measured against the skill of experienced clinicians on a large sample of patients who are difficult to diagnose.

I considered that probability techniques might be applied to the problem of non-toxic goitre, differentiation of which into Hashimoto's disease, simple goitre and thyroid cancer may at times be difficult particularly if the clinical features are atypical. Thus, all these conditions may present with a hard goitre, all may on occasion produce pressure effects and none can be confidently diagnosed by any single laboratory test (13). Furthermore/

Furthermore it is important when faced with a patient with non-toxic goitre to make a correct diagnosis as the treatment of the above conditions differs. While thyroidectomy is often the treatment of choice for thyroid cancer, surgery is usually unnecessary and may result in hypothyroidism in patients with Hashimoto's disease. Lifelong thyroxine is the treatment of choice in the latter group in contrast to the patients with simple goitre who at best benefit only from short courses of thyroxine.

In this part of the thesis I present details of how I constructed a probability matrix for the differential diagnosis of these 3 conditions. The diagnosis of the patients whose data formed this matrix was confirmed by histological examination of thyroid tissue. Using this matrix I calculated the most probable diagnosis for a further group of patients employing two slightly different applications of probability theory. An Elliot 803 automatic digital computer was employed for computation of the diagnosis. These diagnoses were then compared with each other, with a clinician's diagnosis and with the final diagnosis established either by histology, response to therapy or results of long term follow up.

DESCRIPTION OF PATIENTS STUDIED AND METHODS

Patients studied

(a) In Construction of a probability matrix

Fifty-one patients with simple goitre, † 53 patients with Hashimoto's disease and 51 patients with thyroid cancer * were studied. The majority of these patients had been referred to the Thyroid Clinic associated with the University Department of Medicine in the Royal Infirmary, Glasgow. In all patients the diagnosis was confirmed by histological examination of thyroid tissue obtained at operation or biopsy. All of these patients were personally examined by myself apart from 23 patients with Hashimoto's disease who attended the Western Infirmary, Glasgow. I thank Professor Sir Edward Wayne for permission to study these patients. Details of all of these patients are shown in Appendix A (p.412).

Examination of each of the histological sections of the thyroid left no doubt as to the diagnosis in any of the patients. The criteria for the histological diagnosis of Hashimoto's disease were those of Joll (16). In the patients with simple goitre several of the sections showed the minor degree of aggregation of chronic inflammatory cells not infrequently described in simple goitres (17) but

Footnote:

† The term "simple goitre" includes simple goitre, colloid goitre and nodular goitre. These are all stages of the same pathological process (14,15)

*/

* The term "thyroid cancer" includes papillary, follicular and anaplastic carcinoma of the thyroid gland. It was not possible to collect a sufficiently large series of each type to allow them to be considered as separate entities.

but these were not of sufficient severity to cause confusion with Hashimoto's disease. Minor degrees of chronic thyroiditis were likewise seen in many of the patients with thyroid cancer. However severe and extensive chronic thyroiditis was seen in only two patients in whom the primary diagnosis both on clinical and histological grounds was thyroid cancer.

Forty-nine of the patients with Hashimoto's disease were female and four were male; the mean age of these patients was 45.3 years (range 27 to 78 years). Of the patients with simple goitre 49 were female, 2 were male and the mean age was 35.2 years (range 16 to 71 years). Thirty-nine patients with thyroid cancer were females and 12 were males. The mean age of this group was 61.7 years (range 47 to 82 years).

(b) In evaluation of the calculated diagnosis

A further 89 patients attending the same Thyroid Clinic were studied. Details of these patients are supplied in Appendix B (p 464). The diagnosis was confirmed histologically in 49 patients, 21 with Hashimoto's disease, 9 with simple goitre and 19 with thyroid cancer. In 22 patients with Hashimoto's disease and in 17 patients with simple goitre the diagnosis was considered unequivocal on the results of a comprehensive assessment of the clinical features, results of laboratory studies,/

studies, results of follow up observations and the response to treatment. Thus for the purpose of this study either the comprehensive assessment or the histological diagnosis was considered the "final" diagnosis. The diagnosis made by the clinician or by calculation was said to be correct if it agreed with the final diagnosis.

Of the patients with Hashimoto's disease in this group, 41 were female, 2 were male and the mean age was 46.7 years (range 25 to 73 years). The patients with simple goitre comprised 26 females and one male with a mean age of 34.8 years (range 18 to 73 years). Seven of the patients with thyroid cancer were male and 12 were female; the mean age was 59.2 years (range 39 to 79 years).

Clinical and Laboratory Studies

In addition to the age of the patients the following symptoms were recorded: duration of the goitre, presence or absence of discomfort, pain, hoarseness, choking or tightness (classified as one symptom), cough or stridor (classified as one symptom), dysphagia and history of recent increase in size of the goitre. In hypothyroid patients hoarseness was not scored as a symptom. Recent increase in size was said to be present when the goitre had increased in size in the preceding six months.

The clinical signs noted on examination of the patients were:/

were: clinical status, whether euthyroid, hypothyroid or hyperthyroid; the size of the thyroid gland; its consistency; whether it was nodular or was diffusely enlarged and the presence or absence of a pyramidal lobe; fixation to surrounding tissues, cervical lymph nodes and laryngeal palsy.

No attempt was made to make more subtle distinction of degrees of consistency than the three categories soft, firm or hard. It was considered unlikely that greater discriminating power would result from less easily appreciable classifications and in practice this is how the majority of clinicians record the consistency of a goitre. Goitre size was recorded as small (approximately 50 - 100 G.), large (approximately 100 - 200 G.), or very large (greater than 200 G.). In all patients the clinical status was assessed using the criteria described by Wayne (18). Laryngeal palsy was diagnosed by indirect laryngoscopy.

The laboratory investigations performed were as follows: the thyroidal uptake of radioiodine (^{131}I) was measured 24 hours after an oral tracer dose of 25 uc. ^{131}I. Serum protein-bound ^{131}I ($PB^{131}I$), and butanol extractible iodine ($BE^{131}I$) were measured at 48 hours (19).

The discharge of accumulated ^{131}I following the oral/

oral administration of potassium perchlorate ($KClO_4$) was studied. Details of the techniques of study used have been previously described (19,20). The test was said to be positive when either 10 per cent of the accumulated ^{131}I was discharged 40 minutes after $KClO_4$ administration or 12 per cent after 60 minutes.

Serum protein-bound stable iodine ($PB^{127}I$) measurements were performed by the method of Farrell and Richmond (21).

Serum globulin determinations, electrophoresis and serum flocculation tests (thymol turbidity and zinc sulphate turbidity) were carried out using standard laboratory procedures (22,23). The erythrocyte sedimentation rate (E.S.R.) was determined by the Westergren method.

The precipitin test for antithyroglobulin and the complement fixation test for antimicrosomal thyroid auto-antibodies (C.F.) test were performed by the methods described by Goudie, et al (24) and Buchanan, et al (25). The specificity of the C.F. test for thyroid tissue was checked using saline extracts of liver and adrenal gland.

Theoretical basis for the methods

Two approaches were used, based on the concepts of Bayesian/

Bayesian probability (4,10,26) and likelihood (27) respectively. Those who dislike the use of these terms which are admittedly a subject of controversy among professional statisticians and others (28) may prefer to think of the quantities concerned as frequency ratios. In each method the assumption was made that the population being studied consisted entirely of patients suffering from either Hashimoto's disease, simple goitre or thyroid cancer. The general theory of the method follows.

First approach (Bayesian probability)

Suppose that in past experience, out of a total of N_{IJ} patients with an established diagnosis of disease I who had been submitted to test J, $N_{IJK(J)}$ responded with result K(J), the subscript to this latter index showing that the nature of the result depended on the test. Also let N_I represent the number of patients having an established diagnosis of diseases I, and N the total number of patients.

In the study I could have values 1,2 or 3 corresponding to Hashimoto's disease, simple goitre and thyroid cancer respectively, J could have values in/

in the range 1 to 30 and K(J) values in the range 1 to 3. The test and result numbers are shown in table I (p.349). For the purposes of this study a test means either a symptom, sign or laboratory result.

Assuming that a new patient has been drawn from the same population as the others the chance that he or she has disease I on the basis of results $K(J_1)$, $K(J_2)$ ..... $K(J_n)$ for tests J_1, J_2 ..... J_n is taken as

$$(1) \qquad \frac{N_I}{N} \cdot \frac{N_{IJ_1K(J_1)}}{N_{IJ_1}} \cdot \frac{N_{IJ_2K(J_2)}}{N_{IJ_2}} \cdots\cdots \frac{N_{IJ_nK(J_n)}}{N_{IJ_n}}$$

$$\div \sum_{I=1}^{3} \frac{N_I}{N} \cdot \frac{N_{IJ_1K(J_1)}}{N_{IJ_1}} \cdot \frac{N_{IJ_2K(J_2)}}{N_{IJ_2}} \cdots\cdots \frac{N_{IJ_nK(J_n)}}{N_{IJ_n}}$$

In Bayesian theory $\frac{N_I}{N}$ would be called "prior probability" for disease I. The function represents the chance of drawing at random from the population a patient with disease I. The individual /

individual ratios typified by $\frac{N_{IJK(J)}}{N_{IJ}}$ would be regarded as the probability of a patient with disease I producing result K(J) for test J.

As will be discussed more fully later prior probabilities change depending on how patients are selected for study. Thus practical difficulties are encountered when an attempt is made to calculate the prior probability of occurrence of a goitre.

Second approach (relative likelihood)

This approach uses the same entities as does Bayesian probability but the interpretation is somewhat different. For a discussion of the philosophical differences between the two points of view the reader is referred to Kendall and Stuart (27). The main difference from the mathematical standpoint is that the prior probability terms $\frac{N_I}{N}$ (I = 1,2 and 3) are omitted. Thus the chance that a patient has disease I when results $K(J_1)$, $K(J_2)$ ..... $K(J_m)$ are observed for tests J_1, J_2 ..... J_m is now taken to be

$$(2) \qquad \frac{\frac{N_{IJ_1K(J_1)}}{N_{IJ_1}} \cdot \frac{N_{IJ_2K(J_2)}}{N_{IJ_2}} \cdots\cdots \frac{N_{IJ_mK(J_m)}}{N_{IJ_m}}}{\sum_{I=1}^{3} \frac{N_{IJ_1K(J_1)}}{N_{IJ_1}} \cdot \frac{N_{IJ_2K(J_2)}}{N_{IJ_2}} \cdots\cdots \frac{N_{IJ_mK(J_m)}}{N_{IJ_m}}}$$

Since the denominator of this fraction is the same for all the diseases being considered this expression may be written as

$$(3) \qquad K \left[\frac{{}^{n}LJ_1 K(J_1)}{{}^{n}LJ_1} \cdot \frac{{}^{n}LJ_2 K(J_2)}{{}^{n}LJ_2} \cdots\cdots \frac{{}^{n}LJ_m K(J_m)}{{}^{n}LJ_m} \right]$$

The expression in brackets in (3) is called the likelihood of I given $K(J_1)$ ..... $K(J_m)$. In the computer programme it was found convenient to express the score given by (3) by scaling results so that the maximum for any set of diagnoses had a value of 100 per cent. This scaled quantity was called the relative likelihood.

Selection of further tests

Once an initial diagnosis has been calculated it is possible then to select which remaining tests (usually laboratory investigations) are most likely to be worthy of study to enable one to reach a diagnosis. This is done by calculating the discriminating power of each of the remaining tests for the three diseases and expressing the results as a percentage value of the highest discriminating power.

As the mathematical notation for the simple reasoning behind/

behind this calculation is fairly complex, Table 2 has been constructed to aid the reader in following this reasoning. (see p.357)

Let DP_{J_1} and DP_{J_2} be the discriminating power of two tests J_1 and J_2. Let J_1 have two possible outcomes J_1X and J_1Y. Let J_2 have three possible outcomes J_2X, J_2Y, J_2Z (Table 2).

$P_{J_1X \mid h}$ represents the probability of finding the result J_1X in a patient with Hashimoto's disease, $P_{J_1X \mid s}$ the probability of finding result J_1X in a patient with simple goitre, etc.

Consider test J_1. The discriminating power will be a function of the extent to which the probabilities for the possible results J_1X, J_1Y and J_2X, J_2Y and J_2Z differ among the three diseases. If,

$$(4) \qquad P_{J_1X \mid h} = P_{J_1X \mid s}$$

then the occurrence of the result J_1X will not distinguish between Hashimoto's disease and simple goitre, since the likelihood of this outcome is the same for both diseases. Similarly, if

$$(5) \qquad P_{J_2Y \mid h} = P_{J_2Y \mid s} = P_{J_2Z \mid c}$$

if/

if test J_2 gave result J_2Y, it would not be possible on the basis of this result to distinguish between the three diseases.

This would appear to lead to the conclusion that if all the possible differences of probabilities are evaluated for each test

e.g. $(P_{J_1X|h} - P_{J_1X|s})$, $(P_{J_1X|h} - P_{J_1X|c})$, $(P_{J_1X|s} - P_{J_1X|c})$ etc. and all these differences are added together for each test, a measure of the discriminating power of the test will result. However, the differences above will give different results, depending on the order in which the subtractions are made. Since the order should be immaterial, distinguishing between Hashimoto's disease and simple goitre being the same as distinguishing between simple goitre and Hashimoto's disease, the modulus of each difference is used (i.e. the numerical value, ignoring any negative arithmetic sign), and these are added together. So for example, on this basis, the discriminating power of the test J_1 would be:-

$$(6)\quad DP_{J_1} = \left|P_{J_1X|h} - P_{J_1X|s}\right| + \left|P_{J_1X|h} - P_{J_1X|c}\right| + \left|P_{J_1X|s} - P_{J_1X|c}\right| + \left|P_{J_1Y|h} - P_{J_1Y|s}\right| + \left|P_{J_1Y|h} - P_{J_1Y|c}\right| + \left|P_{J_1Y|s} - P_{J_1Y|c}\right|$$

and for J_2:-

$$(7)\quad DP_{J_2} = \left|P_{J_2X|h} - P_{J_2X|s}\right| + \left|P_{J_2X|h} - P_{J_2X|c}\right| + \left|P_{J_2X|s} - P_{J_2X|c}\right| + \left|P_{J_2Y|h} - P_{J_2Y|s}\right| \ldots\ldots\ldots\ldots\ldots\ldots \left|P_{J_2Y|s} - P_{J_2Y|c}\right|$$

The/

The test for which DP is largest is taken to possess best discriminating power between the three conditions. The discriminating power of each test was expressed as a percentage of that of the test with highest discriminating power. Rybowski and Franklin (29) have used an approach similar to this for calculation of tests likely to be of value in identification of bacteria.

It can be shown that the procedure is analogous to evaluating distances in a Euclidean space in which the co-ordinates are probabilities of the various outcomes. Such an idea is not new. Tanimoto (30) used a logarithmic measure of distance in a space which had co-ordinates representing probabilities. In this study, it was not felt necessary to introduce this degree of complication.

(1) Construction of a probability matrix The data (Appendix A p.412) collected on the initial 155 patients who were used to form the probability matrix consists of two kinds. The first kind, the discrete variables, consist of tests which have definite "yes" or "no", "positive " or "negative" results. The possible outcomes of these tests such as presence or absence of fixation of the goitre, positive or negative $KClO_4$ discharge test exist in mutually exclusive classes. The second kind of data exists as continuous variables where the outcome/

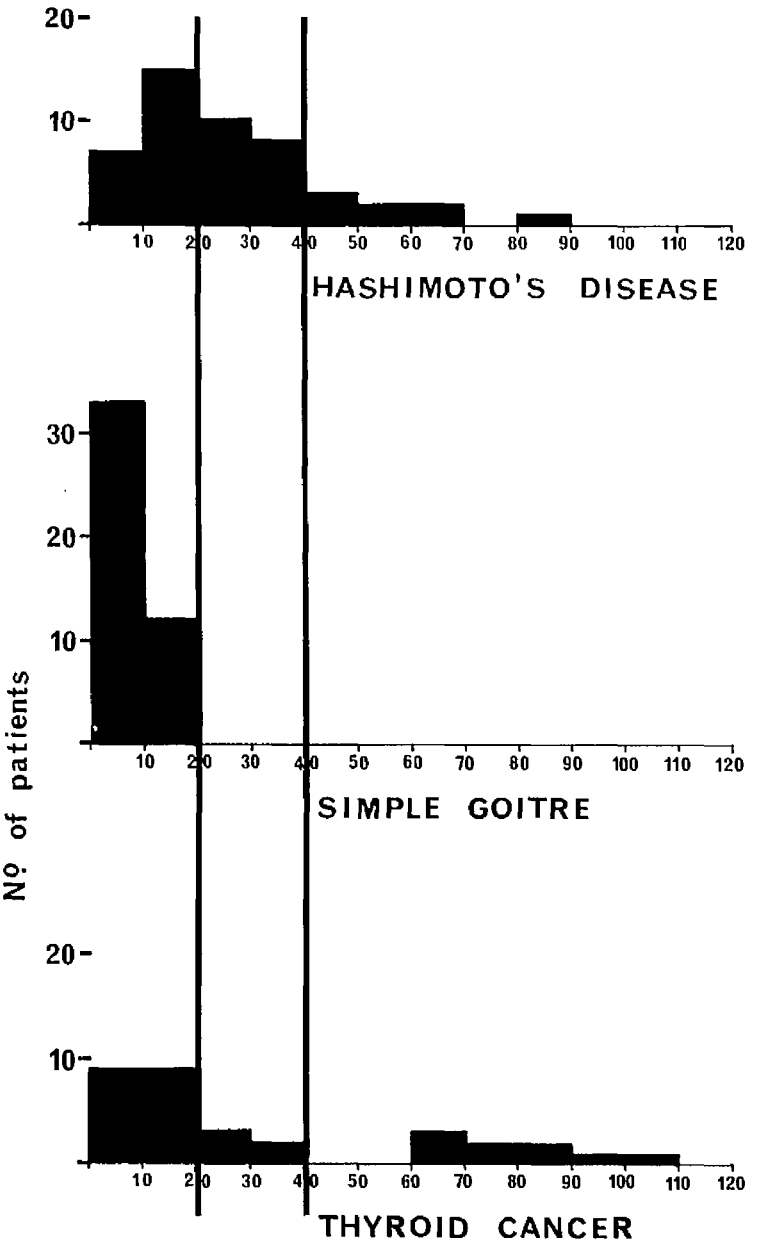

FIGURE 1 The construction of three outcomes for the test J9 (ESR)

outcome of a test may range from zero to 100 or more (e.g. E.S.R.). Continuous variables may be treated as such (10) or alternatively the range of possible values for the test can be divided into a number of mutually exclusive classes thus making the data discrete. The second method of dealing with continuous variables was adopted in this study. Figure 1 shows how the data on the E.S.R. can be transformed into discrete variables. A frequency histogram of the number of patients with each condition having E.S.R.'s in the range 0 - 10, 11-20, 21-30 etc. was constructed. These histograms were compared and it was seen that the best arbitrary separation of the three diseases was obtained when the E.S.R. was considered in the three mutually exclusive classes 0 - 20, 21 - 40 and $>$ 40. Similar frequency histograms were constructed for the other continuous variables and from a consideration of these, arbitrary classes were then chosen which best separated the three diseases from each other.

The probability matrix shown in Table 1 (p.349) was constructed by recording the number of patients with each disease who gave a certain value for each test and had the test performed. As an example 18 of the 48 patients with Hashimoto's disease tested were found to have an/

FIGURE 2 The Elliott 803 digital computer. The drums which take magnetic tape are on the far side of the room, the control desk in the centre of the room.

FIGURE 3 The teleprinter used in this study.

an E.S.R. in the range 21-40 mm/hour. This represents 37.5% of the population of patients with Hashimoto's disease tested and this figure is entered in the probability matrix as 0.3750. Table 3 shows the number of patients who supplied data from which the figures in the probability matrix were derived. (p. 359)

Assessment of Prior Probabilities

The diagnosis in 300 consecutive cases of goitre attending the Thyroid Clinic at Glasgow Royal Infirmary was Hashimoto's disease in 29, simple goitre in 268 and thyroid cancer in 3. The ratio of prior probabilities of occurrence for these three diseases was accordingly taken to be 10: 89: 1.

Computer Specifications

The Elliott 803 medium speed digital computer was used to compute the diagnoses in this study. It has 8192 words of high speed storage each word having a capacity of 39 bits (about 12 decimal digits), and an automatic floating point unit. Output can be either via punched paper tape, punched cards, or on line printer and input via either punched paper tape or punched cards. In this study punched paper tape was used both for input and for output. Figs. 2 and 3 show the Elliott 803 machine and its memory store.

Procedure/

Procedure

The signs recorded for each patient were indicated on a proforma sheet by ringing the appropriate code words. The data on the proforma sheet was transferred to paper tape by punching. A paper tape containing details of the programme or list of instructions the machine had to follow in calculating diagnoses was first fed into the Elliott 803 computer. I had a great deal of assistance from Mr. D. Franklin, M.R.C. Computer Services Centre, London, in writing the programme to meet my requirements in this study. The programme which was written in Elliott 803 autocode is shown in Appendix C (p.490). Anyone wishing to repeat this work and not having an Elliott computer might be better to rewrite the programme from scratch in Algol or Fortran rather than try to adapt it for a machine using these or other languages.

After the programme had been fed in came a tape containing details of the probability matrix (Table 1 p.349). Finally the tape containing data on the patient was fed in and the output containing the computer diagnosis was read off from a direct line teleprinter attached to the machine. On p.361a, Table 4 shows a typical computer print out. The term "Prac. Opt. Pat." refers to an attempt which I made to calculate/

calculate how closely the disease pattern of a particular patient fitted the classic pattern of each of the three diseases as they existed in the computer's memory. The abbreviation stands for "Fractional Optimum Pattern". In addition I had theoretical grounds for believing that it might be of value in showing that a patient had neither of the three diseases under consideration. Unfortunately neither of these hopes were fulfilled by experiment and I shall not discuss the Fractional Optimum Pattern further.

Rather than use solely my own observations on patients to test the efficacy of my method of computer assisted diagnoses, I recorded on the proforma also the observations of several clinicians experienced in diseases of the thyroid gland as they first saw the patients at the thyroid clinic. I also took their diagnosis, once the results of laboratory studies were available, as the clinical diagnosis. In this way it was possible for me to make a clinically realistic appraisal of the method.

RESULTS

Tables 5(p.362), 6(p.370) and 7(p.375) show the results obtained for each of the 89 patients when diagnoses were computed using methods based on Bayesian probability. Tables 8(p.379), 9(p.388) and 10(p.393) show the results obtained when the relative likelihoods of diagnoses were computed. A comparison with the clinician's diagnosis for each individual patient is also included in these tables. Tables 5 and 8 refer to patients in whom the final diagnosis was Hashimoto's disease, Tables 6 and 9 to patients in whom the final diagnosis was simple goitre and Tables 7 and 10 to those who were finally thought to have thyroid cancer.

In addition the results have been synopsised in two contrasting fashions for ease of reference. Tables 11(p. 397) and 12(p.398) show a short summary of the results without making reference to individual patients and these two tables between them enable a quick idea to be gained of the relative performance of clinician and machine. Tables 13 - 15 (. 400-4) show a different way of summarising the results. Here correct and incorrect diagnoses by clinician and machine for each of the three diseases are presented with reference to individual cases/

cases represented as case numbers. The actual probabilities or likelihoods calculated for any case can be found by referring to the appropriate Table (Tables 5 - 10).

I PATIENTS WITH A FINAL DIAGNOSIS OF HASHIMOTO'S DISEASE

There were 43 patients in whom a final diagnosis of Hashimoto's disease was made Table 5(p.362), Table 8(p.379), Table 11(p.397) and Table 12(p.398). Where thyroid cancer was suspected the calculated diagnosis was arbitrarily accepted as being unequivocal if the probability or likelihood of the leading diagnosis on the computer print out was computed as being three times greater than the next possibility on the list of differential diagnoses. For instance, although the computed likelihoods of diagnoses for Case 173 using relative likelihood were Hashimoto's disease 100 per cent, thyroid cancer 73 per cent, and simple goitre 0.01 per cent (Table 8p.379) and although Hashimoto's disease was in fact the final diagnosis the computer calculated diagnosis in this case was judged "wrong" because insufficient separation of Hashimoto's disease from thyroid cancer was obtained. When the diagnosis was computed using Bayesian probability (Table 5p.362) the results were Hashimoto's disease 93.01 per cent probability, thyroid cancer 6.82 per cent probability and simple goitre 0.15 per cent probability. Hashimoto's/

Hashimoto's disease was approximately 14 times more likely than thyroid cancer and Bayesian probability was accordingly judged to have given a correct diagnosis in view of the degree of separation obtained between Hashimoto's disease and thyroid cancer.

In other cases where thyroid cancer did not figure prominently in the differential diagnosis, the disease which was computed as most likely was adopted as the unequivocal computed diagnosis irrespective of the likelihood or probability calculated for the remaining possibilities.

The clinician was classified as having made a wrong diagnosis when he mistakenly took a course of action which under normal circumstances dealing with a typical case of the disease he would not pursue. For example when he arranged thyroidectomy or thyroid biopsy for a patient on suspicion of thyroid cancer and the histological diagnosis and subsequent course of the patient indicated Hashimoto's disease, he was accepted as having made a wrong diagnosis.

(a) Patients in whom the clinician made the correct diagnosis

These patients comprised a group of 28.

Diagnosis computed using relative likelihood. See Table 8(p.379) and Table 12(p.398).

The computer calculated diagnosis agreed with the clinician's diagnosis/

diagnosis in 26 of these cases. Most patients presented little clinical difficulty and this is reflected in the very high likelihoods computed for Hashimoto's disease compared with the extremely low likelihoods computed for simple goitre and thyroid cancer. A typical case History from this group is quoted as an example.

Case 185 - Mrs. A.G.

This 30 year old housewife presented with a 9 month history of goitre which had increased recently in size. She had experienced mild lethargy and a disinclination to do her household duties but had noticed no other symptoms suggestive of hypothyroidism. Her goitre was painless and occasioned her no discomfort. She gave no history of dysphagia, choking or tightness, nor had she a cough.

Examination revealed a placid woman with a cool dry skin, and slight facial puffiness. The thyroid gland was slightly enlarged and easily palpable on account of its nodularity and firmness. The gland moved on swallowing and was not fixed to the surrounding tissues. A pyramidal lobe could not be palpated.

No cervical lymph nodes were palpable and indirect laryngoscopy revealed normal movement of the vocal cords on phonation.

Laboratory/

Laboratory investigations showed the following: E.S.R. 10 mm. in the first hour, precipitin test positive, C.F. test positive, thymol turbidity 1.5 Maclagan units, 48 hour $PB^{131}I$ 0.13 per cent of dose per litre of plasma, $PB^{127}I$ 2.1 ug per 100 ml; there was no radiological evidence of tracheal compression or deviation.

Comment:

While this patient presents a fairly typical picture of Hashimoto's disease which would be recognised by most clinicians, she was by no means a classical case. Thus her goitre was nodular rather than diffuse; she had a normal E.S.R. and thymol turbidity, nor did she demonstrate significant amounts of $PB^{131}I$ at 48 hours. Nonetheless the details given were sufficient for the likelihoods of diagnosis to be calculated as Hashimoto's disease 100 per cent, simple goitre 0.00 per cent and thyroid cancer, 0.00 per cent.

In two of the 28 patients in this group the computer calculated diagnosis agreed with the clinical diagnosis but did not give a sufficiently clear-cut separation between Hashimoto's disease and thyroid cancer. While the likelihoods of Hashimoto's disease being the correct diagnosis were calculated for Cases 220 and 222 (Table 8 p.379) to be 100 per cent, thyroid/

thyroid cancer was calculated as being 67 and 69 per cent likely respectively. These two patients were therefore considered to be incorrectly diagnosed by computation as insufficient separation existed between cancer and Hashimoto's disease.

Diagnosis computed using Bayesian probability
See Table 5 (p. 362) and Table 11 (p. 397)

Here the computer calculated diagnosis also agreed with the clinician's diagnosis in 26 of the Cases. Cases 220 and 222 were among the patients in whom the calculated diagnosis was now correct. The reason why these two patients had a diagnosis calculated incorrectly using relative likelihood and correctly using Bayesian probability deserves brief comment now and will also be discussed later.

As previously explained Bayesian probability and relative likelihood differ from each other only insofar as the former takes account of the prior probabilities of any patient having Hashimoto's disease, simple goitre and thyroid cancer while the latter does not. The ratio for these prior probabilities is 10: 89: 1 respectively. When the ratio of the relative likelihood to be Hashimoto's disease 100 per cent, simple goitre 0.00 per cent and thyroid cancer 67 per cent (Case 220 Table 8 p. 379) computing by Bayesian probability will alter this ratio according to the ratio of the prior probabilities of occurrence of the three diseases and the probabilities/

probabilities become 93.7 per cent, 0.00 per cent and 6.29 per cent respectively. Diagnoses computed from relative likelihood and Bayesian probability may therefore occasionally differ.

In two of these patients the computer calculated diagnosis was incorrect. Simple goitre (74.56 per cent probability) was computed to be more probable than Hashimoto's disease (25.22 per cent probability) in Case 166 (Table 5p.362). In Case 176 simple goitre was computed to be 66.64 per cent probable and Hashimoto's disease was 33.31 per cent probable.

(b) Patients in whom the clinician made an incorrect diagnosis

There were 15 patients in this group.

Diagnosis computed using Relative likelihood
See Table 8(p.379) and Table 12(p.398)

In 12 of these patients the computer calculated diagnosis agreed with the final diagnosis. (Cases 156,158,159,160,161,162, 165,169,171,174,175,177 Table 8(p.379). In most of the patients in this group the clinician probably allowed himself to be unduly swayed by one feature in the history or examination and paid little or no attention to other features which might have led him to the correct diagnosis. In certain instances lack of support from tests which he expected to substantiate his clinical diagnosis (e.g. Case 156) had the effect of dissuading him from the correct diagnosis and led him to a faulty conclusion. The following two patients illustrate these points.

Case 158 - Mrs. M.W./

Case 158 - Mrs. M.W.

A 52 year old housewife presented with a goitre of 6 years' duration which had shown some increase in size in the preceding 5 months. She had experienced some coughing and the sensation of choking but had had no dysphagia or hoarseness. She had no complaint of discomfort or pain in the region of the thyroid gland.

Examination revealed a cheerful woman who was clinically euthyroid. The thyroid gland was small, extremely hard, and nodular but was not fixed to the surrounding tissues and moved easily on swallowing. A pyramidal lobe could not be palpated and the cervical lymph nodes were not palpably enlarged.

Laboratory studies gave the following results: E.S.R. 52 mm. in the first hour. Thymol turbidity 3.9 MacLagan Units, thyroidal 24 hour ^{131}I uptake 68 per cent of dose, 48 hour $PB^{131}I$ 1.01 per cent of dose per litre of plasma, $BE^{131}I$ 93.6% of $PB^{131}I$. Precipitin test was negative.

A diagnosis of thyroid cancer was made. Histological examination of the removed gland showed the appearances of Hashimoto's disease throughout the whole of the thyroid gland and the patient has remained well since her operation on thyroxine therapy.

Comment:

This was a very hard thyroid gland and because of this one/

one fact there was little doubt in the mind of the clinician that he was dealing with cancer. It is difficult to say why Hashimoto's disease was not given more thought in the differential diagnosis but it was hardly considered. A negative precipitin test does not exclude Hashimoto's disease by any means and the raised E.S.R., thymol turbidity and 48 hour PB^{131}I are found more commonly in Hashimoto's disease than in cancer. This case illustrates admirably how one clinical feature may distract the clinician's attention from the overall clinical picture and lead him to a false diagnosis.

Case 156 - Mrs. M.S.

This 44 year old housewife presented with a goitre of 3 month's duration but did not complain of increase in size since the goitre was first noticed. There had been no pain or discomfort in the gland and there was no complaint of dysphagia, choking or hoarseness.

Examination showed a placid woman with a pulse of 72 per minute. Hair was normal in texture and the skin was coarse but warm. The thyroid gland was firm and nodular and small. It was not fixed to surrounding tissues and no pyramidal lobe could be palpated. Cervical lymph nodes were not enlarged.

It was thought possible at this stage the patient might have Hashimoto's disease and indeed the relative likelihoods of this/

this diagnosis by computation from the results of clinical examination alone are Hashimoto's disease 100 per cent, thyroid cancer 0.27 per cent and simple goitre 0.23 per cent.

Laboratory investigations showed the following: precipitin test negative, thymol turbidity 14 Maclagan units, serum globulin 3.6 G. per 100 ml., thyroidal ^{131}I uptake at 24 hours 62 per cent dose, 48 hour PB^{131}I 0.19 per cent dose per litre of plasma.

In view of the negative precipitin test and the normal value for the 48 hour PB^{131}I, the initial impression was reversed and a diagnosis of simple goitre was made. The calculated diagnosishowever was Hashimoto's disease 100 per cent, simple goitre 0.00 per cent and thyroid cancer 0.00 per cent. Histology of the gland showed typical changes of Hashimoto's disease.

Comments:

This is an interesting Case for it demonstrates the inability of the clinician to deal adequately with the many variables which must all be considered in arriving at a correct diagnosis. It also clearly demonstrates that rigidly held ideas about which features should or should not be found in any one disease may lead the clinician from the correct diagnosis if these features are missing. Thus the clinician already having a suspicion of the correct diagnosis relinquished the idea when the precipitin test was found to be negative and the/

the 48 hour ^{131}I normal. No overlooked, or failed to give proper weight to the very high thymol turbidity in this case. There are no patients with simple goitre in the probability matrix (Table 1 p.349) whose thymol turbidity value is greater than 5 Maclagan units and it is probably also true that such a finding is uncommon in patients with simple goitre. Examination of the probability matrix shows too that it is not uncommon for a patient with Hashimoto's disease to have a negative precipitin test and a normal ^{131}I at 48 hours. Consideration of these points would have made the diagnosis of Hashimoto's disease very likely in this patient had the calculation thought in this manner.

In the remaining three of this group of 15 patients both the clinical and the calculated diagnoses were wrong (Case 157 170 and 173). These patients had rather atypical forms of Hashimoto's disease insofar as the gland was hard and nodular, the precipitin test was negative, there were no serum protein disturbances and the radiodine tests were unhelpful. As already mentioned the correct diagnosis was computed for Case 173 but this was not taken to be a sufficiently more likely possibility than thyroid cancer (likelihood 73 per cent) for it to be of clinical value and accordingly this calculation has been classified as giving a wrong diagnosis.

Diagnosis computed using Bayesian probability.
See Table 5(p.362) and Table 11(p.397)

The/

The results of calculations using Bayesian probability agree closely with those obtained using relative likelihood. Thus in 12 of the patients the computer calculated diagnosis agreed with the final diagnosis and disagreed with the clinical diagnosis. (Cases 156,158,159,160,161,162,165,169, 173,174,175 and 176 Table 5p.362). Case 173 in which the diagnosis was insufficiently clear-cut and therefore erroneous when computed by relative likelihood was correctly diagnosed using Bayesian probability. The remaining three patients who had erroneous diagnoses computed were Cases 157 and 170 (as also occurred when relative likelihood was used) and Case 171 who had been diagnosed correctly using relative likelihood.

II PATIENTS WITH A FINAL DIAGNOSIS OF SIMPLE GOITRE

There were 27 patients in this study who had a final diagnosis of simple goitre Table 6(p.370), Table 9(p.388), Table 11(p.397) and Table 12(p.398).

(a) Patients in whom the clinician made the correct diagnosis

There were 25 patients in whom the clinician made a correct diagnosis.

Diagnosis computed using relative likelihood
See Table 9(p.388) and Table 12(p.398)

Here the calculated diagnosis agreed with the clinician's diagnosis in 22 Cases. In three patients (Cases 181, 184 and 191) the calculated diagnosis did not agree with the clinical diagnosis./

Case 181 - Mrs. M. McV.

A housewife, 43 years of age, complained of exertional dyspnoea dating from an attack of acute bronchitis four months previously. She had had chronic bronchitis for 20 years manifested by cough and mucopurulent sputum especially during the winter months. Cough had been worse recently and she had also noticed stridor. She had had a goitre since the age of 16 years but had not noticed any recent increase in size. She had been hoarse but had not experienced dysphagia. There had been no pain or discomfort in the region of her thyroid gland.

Examination revealed a euthyroid woman with inspiratory and expiratory stridor and a wheeze.

The thyroid gland was hugely enlarged, soft and nodular and was not fixed to the surrounding tissues. She had a left sided Horner's syndrome which had been present for 15 years. A pyramidal lobe was not palpated and the cervical glands were not enlarged. Examination of the chest showed basal crepitations and fairly widespread rhonchi which were thought to be indicative of an attack of acute bronchitis superimposed on longstanding chronic bronchitis.

Laboratory studies: E.S.R. 29 mm. in the first hour, white blood count 8,400 per cmm. haemoglobin 13.8 G. per 100 ml. Chest x-ray showed congestive changes in both basal regions and/

and marked bilateral upper mediastinal widening consistent with an enlarged thyroid gland. X-ray of tracheal inlet showed tracheal compression. Sputum culture was negative, serum globulins 3.0 G. per 100 ml., thymol turbidity 0.8 Maclagan units and the twenty-four hour thyroidal ^{131}I uptake was 52 per cent of the dose. PB^{131}I at 48 hours was negligible. Indirect laryngoscopy showed the left vocal cord to be practically immobile in the cadaveric position and the right cord moving freely and approximating to it on phonation. Respiratory function tests: vital capacity 2.8 litres, F.E.V. (1 sec.) 1.54 litres. These findings were unchanged after isoprenaline and the results were interpreted as showing evidence of airways obstruction not relieved by bronchodilators.

Comment:

The probability of a patient whose E.S.R. is 28 mm. in the first hour and who has laryngeal palsy, having a simple goitre is extremely remote. Thus thyroid cancer, which is very likely in the presence of laryngeal palsy was the first calculated diagnosis and Hashimoto's disease (likelihood 3.13 per cent) was the second diagnosis (Table 9p. 388).

The clinician on the other hand had information about this patient which allowed him to place much less clinical emphasis/

emphasis on these findings. He knew for example that the rise in E.S.R. might well be secondary to the acute bronchitis. In addition he realised that the patient had had Horner's syndrome for 15 years and that this was presumably due to pressure of the goitre on the cervical sympathetic nerves. As she was still alive 15 years later it was unlikely that thyroid cancer was the diagnosis. After control of her bronchitis the patient was submitted to thyroidectomy on account of the clinical evidence of pressure on the recurrent laryngeal nerve.

This Case illustrates one of the difficulties which may arise in the attempt to calculate a diagnosis. A general approach for dealing with patients in whom dual pathology alters the clinical significance to be attached to any particular feature, does not at the moment suggest itself. Omitting the feature whose significance is questionable from the data from which the diagnosis is to be calculated might conceivably prove of value and in this patient such a procedure allowed the correct diagnosis to be calculated.

Case 191 - Mrs. J.H.

A 32 year old housewife who gave a history of a goitre present for 6 months with no recent increase in size./

size. She had experienced choking but had had neither dysphagia nor hoarseness nor discomfort in the region of her thyroid gland. She did not complain of cough.

Examination showed a somewhat pale woman who was composed and whose skin was warm but dry. The thyroid gland was large, soft and diffusely enlarged. It was not fixed. Neither a pyramidal lobe nor cervical glands could be palpated.

Laboratory studies gave the following results: Thyroidal 24 hour ^{131}I uptake 51 per cent of dose, PB^{131}I at 48 hours 0.02 per cent dose per litre of plasma, serum globulin 2.8 G. per 100 ml., thymol turbidity 2.3 Maclagan units. An X-ray of the tracheal outlet showed evidence of tracheal deviation and compression. The computed diagnosis was Hashimoto's disease.

The clinician was content with the information above to make a diagnosis of simple goitre and this was confirmed by histology when the patient insisted on thyroidectomy because of the choking sensation in her throat.

Comment:

It is possible that this case demonstrates a disadvantage of dividing continuous variables into discrete classes in the construction of the probability matrix. The thymol turbidity and/

and serum globulin are not significantly elevated in this patient. The clinician accepted these results as being reasonably normal and finding a soft goitre with normal ^{131}I studies and no evidence of abnormality in the plasma proteins accepted the obvious diagnosis of simple goitre without further study. The three discrete classes into which the values for the sign, thymol turbidity are grouped in the probability matrix however are 0 to 2, 2.1 to 5 and greater than 5 Maclagan units (Table 1 p. 349). The value 2.3 therefore falls just within the lower range of the second class. Examination of the matrix shows that the likelihoods of simple goitre and Hashimoto's disease when this sign has a value lying in the second class are 11.89 and 27.66 respectively. Thus Hashimoto's disease is approximately twice as likely as simple goitre. The likelihoods for these diseases when the value for the sign lies in the first class are 88.10 and 25.53 respectively and simple goitre is now approximately three times more likely than Hashimoto's disease. The placing of this particular thymol turbidity value in the second class rather than the first class thus makes Hashimoto's disease 6 times more likely than it would have been if the thymol turbidity value had fallen in the first class. If this reasonably normal value had been treated on its merits

it/

it would not have had such a profound effect on the outcome of the calculated diagnosis. Similar considerations apply to the result for the serum globulin level. A solution to these difficulties may be found when more data has been collected for the probability matrix, or when the continuous variables are treated as such (10) rather than being grouped into discrete classes.

Diagnosis computed using Bayesian probability

When the diagnosis was calculated using Bayesian probability simple goitre was calculated to be a much more likely possibility for Case 192 than it had previously been, but the first calculated diagnosis was still wrong. Case 184 was diagnosed correctly. In other respects the results were identical with those obtained using relative likelihood.

(b) Patients in whom the clinician made the wrong diagnosis

There were two patients (Cases 180 and 192) in this group.

Diagnosis computed using relative likelihood
See Table 9(p.388) and Table 12(p.398)

Both the calculated diagnosis and the clinician's diagnosis agreed in these two patients and both were wrong. Both patients presented with symptoms and signs strongly suggestive of thyroid cancer. The following case illustrates the difficulties.

Case 180 - Mrs. F.W./

Case 180 - Mrs. F.W.

This 67 year old widow had had a goitre for 35 years. She presented with a history of noisy breathing and had noticed that her goitre was increasing in size recently. She had had attacks of choking and a tight sensation in her throat but did not complain of dysphagia, hoarseness or tenderness in her thyroid gland.

Examination showed a robust woman with easily audible stridor and a large stony-hard nodular thyroid gland which was firmly fixed to the adjacent tissues. No cervical glands were palpable nor could a pyramidal lobe be felt.

Laboratory investigations: Thyroidal ^{131}I uptake at 24 hours 27 per cent dose, PB^{131}I at 48 hours 0.13 per cent dose per litre of plasma. X-ray of tracheal outlet showed tracheal compression and deviation. Serum globulin 3 G. per 100 ml. Thymol turbidity 0.7 Maclagan units.

A confident clinical diagnosis of thyroid cancer was confounded at operation when the appearances, confirmed by histology, were those of simple goitre.

Comments:

This patient presented an atypical form of simple goitre. It is difficult to see how she could have been diagnosed correctly without thyroid biopsy and both the clinical and computed/

computed diagnosis favoured thyroid cancer.

Diagnosis computed using Bayesian probability

Here the results were identical to those obtained using relative likelihood.

III PATIENTS WITH A FINAL DIAGNOSIS OF THYROID CANCER

In this study there were 19 patients in whom the final diagnosis was thyroid cancer (Table 7p. 375, Table 10p. 393, Table 11p. 397, Table 12p. 398).

(a) Patients in whom the clinician made the correct diagnosis

Diagnosis computed using relative likelihood
See Table 10(p. 393) and Table 12(p. 398)

Here there were 16 patients whose diagnosis calculated by relative likelihood agreed with the clinical diagnosis.

All patients diagnosed correctly by the clinician as having thyroid cancer were also calculated to have thyroid cancer when relative likelihood was used.

Diagnosis computed using Bayesian probability
See Table 7(p.375) and Table 11(p.397)

The results using Bayesian probability were less satisfactory. Thus while 13 patients were calculated to have thyroid cancer, 3 patients (Cases 235, 237 and 242) were calculated to have simple goitre. All of these patients presented with symptoms and signs which were suggestive of thyroid cancer and although some clinical difficulty was encountered/

encountered a correct diagnosis was made by the clinician. In view of these results it is felt that Bayesian probability is inferior to relative likelihood for the purpose of calculating a diagnosis. This point is discussed more fully later.

(b) Patients in whom the clinician made the wrong diagnosis

Diagnosis computed using relative likelihood
See Table 10(p. 393)and Table 12(p.398)

In the three patients in this group (Cases 232, 240 and 241) both the calculated diagnosis and the clinician's diagnosis were wrong. One of these cases is quoted as an example.

Case 232 - Mrs. G.H.

This 45 year old housewife presented with a history of nervousness, palpitations, sweating and slight shortness of breath of many years' duration.

She had had no hoarseness, dysphagia or discomfort in the region of the thyroid gland. There had been no weight loss. Examination showed a nervous woman with cool moist skin and a coarse finger tremor. Pulse was 96 per minute. There were no eye signs of thyrotoxicosis and the patient was not hyperkinetic. The thyroid gland although definitely enlarged was small and fairly nodular with one larger firm nodule in the right lower pole of the gland. The/

The thyroid moved easily on swallowing and was silent. At the right hand side of the thyroid a small firm mobile cervical node was palpable. On investigation the following results were obtained. Thyroidal 24 hour ^{131}I uptake 53 per cent dose. PB^{131}I at 48 hours 0.06 per cent of dose per litre of plasma. E.S.R. 2 mm. in the first hour. X-ray of the tracheal outlet showed no evidence of tracheal compression nor deviation. Thyroxal turbidity 0.7 Maclagan units.

The clinical impression was of a long-standing simple nodular goitre with a larger nodule in the right lower pole of the gland. It was realised that a palpable lymph node was suspicious of thyroid cancer (and it was for this reason that thyroidectomy was undertaken) but it was felt that the most probable diagnosis was simple goitre in view of the mobility and the consistency of the thyroid gland. Histology of the nodule showed a thyroid cancer of mixed papillary and follicular type. The lymph node was almost wholly replaced by secondary differentiated and undifferentiated cancer with central cystic degeneration.

Comment:

It is this type of case which can cause the clinician much/

much difficulty in diagnosis. It is interesting to note that the computer-calculated diagnosis places thyroid cancer fairly high on the list of diagnostic probabilities (simple goitre 100 per cent, thyroid cancer 32.54 per cent, Hashimoto's disease 0.91 per cent Table 10(p.393). Indeed if one accepts the arbitrary criterion that if thyroid cancer is not to be considered as a likely alternative diagnosis it must be less than three times as likely as the first diagnosis, then it is seen that in this case the diagnosis of thyroid cancer was not entirely satisfactorily excluded by the calculated diagnosis lying as it does on the borderline of this range.

Diagnosis computed using Bayesian probability
See Table 7(p.375) and Table 11(p.397)

When diagnoses were computed using Bayesian probability the results were essentially similar to those obtained using relative likelihood. One important difference existed for Case 232. Whereas thyroid cancer was calculated to be a diagnostic possibility in this patient by relative likelihood when Bayesian probability was used it was hardly considered as a possibility (simple goitre 99.52 per cent, thyroid cancer 0.36 per cent, Hashimoto's disease 0.10 per cent).

IV DIAGNOSES WHICH WERE WRONG CONTRASTED WITH DIAGNOSES WHICH WERE MISSED

So/

So far I have classified diagnoses as either "correct" or "wrong". It is obvious that when the diagnostic performance of a clinician is being considered the situation may be more complex than this and less easily definable. For instance although he often considered Hashimoto's disease a likely diagnosis he sometimes felt it necessary to advise either biopsy or thyroidectomy on the suspicion of thyroid cancer. These procedures not only cause the patient great inconvenience but may also on occasion be harmful. Nor would the clinician usually recommend them if he was reasonably certain of the diagnosis. Accordingly where the histology showed Hashimoto's disease the clinician's diagnosis was classified as wrong. However, although it may not be ideal it is nonetheless clinically acceptable to make a wrong diagnosis while considering the possibility of the correct diagnosis. For instance the clinician considered that the diagnosis was most likely to be simple goitre in Case 232 but he advised thyroidectomy. Although his clinical impression was of simple goitre he did not discard the possibility of thyroid cancer. One cannot say that he missed the diagnosis of thyroid cancer. Thus when the clinical usefulness of the calculated diagnosis is being assessed it is important to mention not only the Cases where this was wrong but also to describe how often the correct diagnosis was completely missed by/

by the clinician and by calculation. I have defined a missed diagnosis in this study as one where the clinician did not even consider the possibility of the correct diagnosis as a differential diagnosis or where the wrong diagnosis was calculated to be 10 times more likely than the correct diagnosis. It was felt that this latter figure was reasonable for purposes of comparison between clinical and computed diagnoses for if a clinician considers the possibility of the correct diagnosis as being less than one in 10, it is fair to assume that he has missed the diagnosis.

Table 16 shows the wrong diagnoses analysed in this way. Relative likelihood missed three patients with simple goitre (Cases 181, 182 and 191) who were either diagnosed or had the correct diagnosis at least considered by the clinician. The results for thyroid cancer are particularly important from the clinical standpoint. Calculations using Bayesian probability gave a completely erroneous diagnosis in one patient (Case 232), for whom the clinician considered cancer as a differential diagnosis. The likelihood of thyroid cancer being the diagnosis for this patient calculated by relative likelihood was 32.54 per cent (Table 10p.393) and this draws/

draws attention to the need to consider it in the differential diagnosis. In other words Bayesian probability gave misleading results in this patient, relative likelihood did not. Bayesian probability also missed the diagnosis of cancer in Case 235 who was correctly diagnosed by the clinician. Where thyroid cancer was concerned the diagnostic performance of relative likelihood and clinician was identical.

V SELECTION OF FURTHER TESTS

In cases 156 to 200, only the results of history taking and clinical examination were initially supplied as data to the machine. This allowed equations (6) and (7) (p.174) to be used in these cases to calculate which remaining tests, namely laboratory investigations, were most likely to give a correct diagnosis. The tests selected by calculation were those which a clinician would in most instances have chosen himself. Table 4(p.361a) shows a representative example of the tests calculated for some patients when the results of history and clinical examination were supplied as data to the machine. Once an initial diagnosis had been computed using clinical data, the results of laboratory procedures were then also incorporated and the diagnosis was recalculated using all the information available to the clinician. The results I obtained in the selection of further tests by the machine make me feel that the facilities offered by equations (6) and (7) would be well/

well worth while incorporating into future diagnostic programmes. The approach is as it stands a relatively crude one and some of its deficiencies are discussed later but in the present study the tests which were selected by the machine although obvious next steps for a doctor experienced in thyroid disease may not have been so obvious to a doctor with less experience in this field.

DISCUSSION

It has been suggested that calculated diagnoses produced by digital computers may one day be applicable to a large number of diseases for which there exist many signs and symptoms. Behind this suggestion is the realisation that the clinician of to-day cannot possibly keep abreast of all the new information which is now being published daily in medical literature throughout the world (9). Although wide interest has been expressed in such possibilities (2) the results of few studies have so far been reported and in none have detailed comparisons been made between the diagnosis calculated using probability theory and the clinical diagnosis when discordance existed between them. Thus they do not give the information which a clinician would require before feeling that he could have faith in a computer-calculated diagnosis.

Where two procedures give essentially the same results there is no reason for using one in preference to the other. Where the procedures give differing results then one may be superior to the other and the use of the superior procedure may then become justified (31). This comment applies as much to the formulation of a diagnosis as to any other activity and if techniques for automatic computation of diagnoses are to find wide acceptance in medicine they must be shown to give better results than does the clinician in the face of a difficult/

difficult diagnostic problem.

The advantage of the present study is that a histological diagnosis has always been available where disagreement of opinion between the clinician and computer occurred. In the series of 89 patients disagreement between clinical and computed diagnoses occurred in 17 patients using relative likelihood. In 5 of these patients the clinician's diagnosis was supported by histological examination of thyroid tissue. In the remaining 12 patients the computer-calculated diagnosis was similarly confirmed.

Vishnevsky, Artobolevsky and Bykhovsky (11) dealing with congenital heart disease, have also noted that in some of their patients the computer-calculated diagnosis disagreed with the clinical diagnosis. These authors found that at operation the calculated diagnosis was confirmed. Unfortunately they do not give clinical details of the individual patients nor do they state how often discrepancy of opinion between the clinician and computer occurred.

The concept of a computer being better at diagnosing illness than a clinician is both emotionally and logically unacceptable for in the final analysis it is the scientific ingenuity of the human mind that tells the computer how to perform/

perform these remarkable feats (2) or as a recent leading article in the British Medical Journal (32) put it, "the computer cannot ... produce constructive thought or any basic facts other than those with which it has been programmed".

As shown in Table 10 when the computer was programmed to take account of the prior probabilities of occurrence of the three diseases (Bayesian probability) in the calculation of the diagnosis, three patients with thyroid cancer were misdiagnosed. These patients were diagnosed correctly by the clinician and by computation using relative likelihood. A fourth patient (Case 232) with thyroid cancer in whom this diagnosis was given as a possible differential diagnosis by calculation using relative likelihood and by the clinician was completely misdiagnosed when prior probabilities were used in the calculation. The reason for the poorer results obtained when prior probabilities are used comes from a consideration of how prior probabilities may change depending on the population from which a particular patient is drawn. If he is selected <u>at random</u> from the general population of Great Britian, the chances of his having thyroid cancer are remote, and accordingly the prior probability of thyroid cancer is very small. If he is selected at random from a doctor's surgery the prior probability of his having thyroid cancer becomes somewhat greater. This probability is greater still as one

moves/

moves from a population of patients in a doctor's waiting room to a population of hospital outpatients and from there to a population of patients attending a special clinic for diseases of the thyroid gland. The composition of patients and diseases in these different populations is radically altered by the process of selection.

There is still another way in which selection may change these probabilities relative to each other. In this study patients who occasioned the clinician some diagnostic difficulty were selected for computer calculated diagnosis. Although simple goitre occurs most commonly in a thyroid clinic followed in decreasing frequency of occurrence by Hashimoto's disease and thyroid cancer, when the final diagnoses of patients who occasion diagnostic difficulty are examined it is seen that Hashimoto's disease is the commonest diagnosis, thyroid cancer is next commonest and simple goitre is least common (Table 11 p.397, Table 12 p.398). Therefore the prior probabilities which apply to any patient picked at random from the population attending a thyroid clinic, are erroneous when applied to a particular patient who has been especially selected by reason of the diagnostic difficulty which he presented to the clinician. This would seem to be the explanation/

explanation of the poorer result obtained when diagnoses were calculated using prior probabilities. Even if it were possible to predict a figure for prior probabilities for each disease for any patient presenting diagnostic difficulty to one doctor (for instance from a study of that doctor's past performance) it is not certain that these prior probability rates would hold for another doctor who may be better at diagnosing, for example, thyroid cancer but worse at diagnosing Hashimoto's disease. If diagnoses are being computed routinely for every patient who presents with a non-toxic goitre, prior probabilities based on an estimate of the final diagnoses of a large number of patients attending a thyroid clinic would be valid. If on the other hand, cases are being selected for diagnosis the results of this study suggest that values for prior probabilities should not be included in the computation.

The omission of prior probabilities possesses a particular advantage when one is dealing with non-toxic goitre, for thyroid cancer, a rare disease, then becomes just as likely a diagnosis as simple goitre, whereas with the inclusion of prior probabilities it is 89 times less likely. The safety factor thus included weights the results of the computation towards thyroid cancer and is clinically acceptable; in addition/

addition the diagnosis is then based on clinical findings alone and not on a factor which has nothing to do with them, namely incidence. It was considered that the signs used in the construction of the probability matrix should be derived from patients who had undergone thyroidectomy or thyroid biopsy for only then could one be certain of the validity of the diagnosis and the integrity of the matrix from which diagnoses would be calculated for new patients. It might be argued that patients with simple goitre or Hashimoto's disease who have undergone thyroidectomy or have been submitted to thyroid biopsy can hardly be considered representative of the general population of patients with these diseases and that miscalculation of diagnoses might accordingly result. In some instances a goitre was removed because the clinical picture was atypical and the diagnoses in doubt, in some instances because of pressure symptoms and in some instances for cosmetic reasons. Although thyroidectomy was thus undertaken for different reasons in this series of patients in most of them the reason for operation or biopsy was that in many cases the clinician was in some doubt as to the diagnosis. It is conceivable that if calculations based on data from a probability matrix are to be of value to the clinician facing an atypical or difficult case the data in the matrix should have been derived from patients who themselves have occasioned diagnostic difficulty.

Notwithstanding/

Notwithstanding these considerations there is little doubt that the model used in this study was extremely successful in diagnosing the typical case of each disease.

Inherent in all clinical studies is a large element of observer variation which as Crooks, Murray and Wayne (3) have shown can be reduced but not completely eliminated. No special cognisance was taken of observer error because this study is concerned solely with the interpretation of the history, and physical signs as they were recorded by the clinician and the question of observer error then becomes irrelevant.

The logic behind both of the methods used in this study for the calculation of diagnoses is that of conditional probability theory and one of the major difficulties involved in its application to diagnosis is occasioned by the inter-dependence which may exist between tests. Interdependence may be said to occur between two tests when the probability of occurrence of either of them is affected by the presence or absence of the other. Table 17 (p. 409) illustrates how errors may arise in the calculation of diagnosis when tests are interdependent. Shown is a probability matrix consisting of 5 tests, thymol turbidity, thymol flocculation, zinc sulphate turbidity, cephalincholesterol flocculation and colloidal gold which/

which are interrelated as they all reflect to a greater or lesser degree changes in the serum globulins. For ease of comparison between them the results of the tests are considered in three classes "normal" (I), "slightly abnormal" (II) and "very abnormal" (III). The "collective probability", that is the probability of a patient whose results for all 5 tests lie in the same class is also shown. Because these tests are interdependent a patient who gives for example a class I result to any one of them is liable to give a class I result to any of the other ones irrespective of the disease which he has. The likelihood of a patient with any single class I result having thyroid cancer ranges as shown in Table 17 from 1.2 to 3.9. If all the signs are considered together the likelihood is now 69.2. Therefore when more than one of these interdependent tests is used in calculating a diagnosis the likelihood of thyroid cancer, to cite a specific example, will be calculated as being falsely high if the patient has a class I result to any test.

As Engle (33) has remarked in a closely integrated organism such as a human being, it would be quite remarkable if all of the signs resulting from a single disease process were independent. Warner has tried two approaches to the problem of interdependence of signs. In the first (4) he combined certain signs which he recognised as interdependent and then/

and then considered them as a single sign complex. In the second approach with Nugent and his colleagues (34) he examined the independence of signs by preparing two by two contingency tables for the actual and expected coincidences of 154 possible paired combinations of 13 signs in his patients. Associations were judged to be significant or not significant on the basis of the X^2 test (35). This approach might be clinically unsatisfactory for to say that two signs are interdependent is not to deny that while taken collectively they may give an unduly high estimate of the probability of a disease, they nonetheless both have valid resolving power between two diseases although of a lesser degree than that suggested by their interdependence. Accordingly to disregard one of these signs entirely might result in neglecting clinically relevant information.

Bailey (10) feels that the use of some of the recently developed theory of interactions in contingency tables (36,37) might provide the correct method of approach when one is dealing with interdependence between the discrete variables but it is unlikely that these procedures could be adopted without greatly increasing the complexity of the mathematical model.

In/

In the present study I made an approximation. I considered that the serum flocculation tests were the ones which were likely to be most interdependent as they all reflect changes in the serum globulins. The information obtained from the signs 'thymol flocculation', 'cephalin cholesterol' and 'colloidal gold' was not used in the construction of the probability matrix. When the sign thymol turbidity was used to calculate the diagnosis of a particular patient, the value of the zinc sulphate turbidity was not used and vice versa. All other tests were taken as being independent. The results obtained in the study justify this approximation.

For conditional probability theory to be completely valid not only should all signs be independent of each other but the diseases themselves should be mutually exclusive. Simple goitre and Hashimoto's disease may be accepted as such. While thyroid cancer is known to occur in glands previously the seat of Hashimoto's disease (38,39) this association is uncommon and probably not significant (40,41). The incidence of thyroid cancer in patients with simple goitre is reported by Sokal (42,43) as being less than 0.5 per cent. It is therefore likely for practical purposes that these three diseases can be accepted as mutually exclusive and that large errors will not result from this assumption when techniques based on the theory of conditional/

conditional probability are applied to the calculation of a diagnosis.

It will be apparent that the present studies describe a model for the calculation of diagnosis. There remain many improvements which might be incorporated into future models and which could be of immense value to the clinician. For instance the calculation of the discriminating power of the signs which remain in the matrix could be better tailored to suit the clinician's needs. At present only those signs which best distinguish between all three diseases are picked whereas in many instances the clinical problem is to distinguish between two diseases both of which are quite likely to be the correct diagnosis. One refinement which would be of immense importance concerns the programming of the machine to stop calculating a diagnosis and printing out further differentiating tests to be done once sufficient evidence has accumulated to point unequivocally to one disease. It would be the clinician's responsibility to build into the machine's instructions the definition of the word "unequivocal". This involves a consideration of the next refinement which would entail programming the machine to calculate the level of significance reached between the probability values for the first and second diagnostic possibilities. The clinician could dictate the degree of significance required before the diagnosis could be said to be/

be unequivocal.

The act of diagnosis is a highly complex one which at present defies systematic analysis. It may be that a doctor passes through two stages in arriving at a diagnosis. In one stage he records symptoms and signs and has certain laboratory tests carried out and in the other he evaluates these signs according to his experience. This is probably an oversimplification of the processes involving correct diagnosis for it is equally likely that an initial cluster of symptoms or signs prompts the clinician to search for other features which may be fitted into the pattern which at an early stage he has recognised as being a possible diagnosis. New information strengthens or weakens the pattern impression he has constructed and in turn may lead to the formation of new patterns. These speculations do not preclude the possibility that correct diagnoses could be calculated using methods which although different from the clinician's may be no less logical and are certainly more easily defined than his. The results of this part of the thesis support this contention.

SUMMARY

This part of the thesis described the use of a computer in the diagnosis of non-toxic goitre.

In a study of 53 patients with Hashimoto's disease, 51 with simple goitre and 51 with thyroid cancer in whom the diagnosis had been confirmed histologically, information relating to symptoms, signs and results of laboratory investigations were used to construct a probability matrix consisting of a table of the observed incidence of each piece of information in each of the three diseases. From the data diagnoses were calculated on a computer for a fresh series of 89 patients, (43 with Hashimoto's disease, 27 with simple goitre and 19 with thyroid cancer), using two slightly different applications of probability theory (a) taking account of the existence of prior probabilities of occurrence for each condition and (b) ignoring these factors.

The two diagnoses computed for each patient were compared with each other and with the diagnosis of a clinician experienced in dealing with thyroid conditions. The computer was also used to calculate which laboratory tests would be most likely to give the correct diagnosis once the results of the clinical examination had been supplied as data to the computer.

The/

The results show that diagnoses computed using probability theory are at least as reliable as those of the experienced clinician. Tests selected by calculation were clinically realistic.

Many difficulties remain to be overcome in what is a highly experimental approach to the problem of diagnosis.

1. Ledley, R.S. and Lusted, L.B. (1959a) Science 130, 9

2. Ledley, R.S. and Lusted, L.B. (1959a) Proc. Inst. Radio Engineers 47, 1970

3. Crooks, J., Murray, I.P.C., and Wayne, E.J. (1959) Quart. J. Med. 28, 211

4. Warner, H.R., Toronto, A.F., Veasey, L.G. and Stephenson, R. (1961) J. Amer. med. Ass. 177, 177

5. van Woerkom, A.J. and Brodman, K. (1961) Biometrics 17, 299

6. Masuyama, M. (1963) Rep. statist. appl. Res. Un. Jap. Sci. Engr., 10, 151

7. Overall, J.E. and Williams, C.M. (1963) J. Amer. Med. Ass., 183, 307

8. Payne, L.C. (1963) Wld. Med. Electronics 2, 7

9. Payne, L.C. (1964) Lancet 2, 32

10. Bailey, N.T.J. (1965) Proc. M.R.C. Conf. on Mathematics and Computer Science in Biology and Medicine. 103

11. Vishnevsky, A.A., Artobolevsky, I.I. and Bykhovsky, M.L. (1964) Sci. Wld. 3, 13

12. Spencer, W.A. and Valborn, C.(1965), J. Amer. Med. Ass. 191, 917,

13. Buchanan, W.W., Harden, R. McG. and Clark, D.H. (1965) Brit. J. Surg. 52, 430

14. Spence, A.W. (1952) Brit. med. J. 2, 529

15. Spence, A.W. (1960) Postgrad. med. J. 36, 430

16./

16. Joll, C.A. (1939)
Brit. J. Surg. 27, 351

17. Anderson, J.R., Buchanan, W.W., Goudie, R.B. and Gray, K.G. (1962)
J. clin. Path. 15, 462

18. Wayne, E.J. (1960)
Brit. med. J. 1, 78

19. Murray, I.P.C. and McGirr, E.M. (1960)
Brit. med. J. 1, 838

20. Koutras, D.A., Alexander, W.D., Buchanan, W.W., Crooks, J. and Wayne, E.J.(1960).
Scot. med. J. 5, 331

21. Farrell, L.P. and Richmond, M.H. (1961)
Clin. chim. Acta 6, 620

22. MacLagan, N.F., (1944)
Brit. J. exp. Path. 25, 234

23. Kunkel, H.G., (1947)
Proc. Soc. exp. Biol. (N.Y.), 66, 217

24. Goudie, R.B., Anderson, J.R., Gray, K.G., Clark, D.M., Murray, I.P.C. and McNicol, G.P. (1957)
Lancet, 2 976

25. Buchanan, W.W., Alexander, W.D., Brass, W., Anderson, J.R., Goudie, R.B. and Gray, K.G. (1962)
J. Endocr. 24, 115

26. Jeffreys, H. (1961)
Theory of Probability. 3rd ed. Clarendon Press, Oxford.

27. Kendall, M.G. and Stuart, A. in The Advanced Theory of Statistics. Chas. Griffen and Co. Lond. p.198, (1947).

28. Franklin, D.A.
M.R.C. Computer Services Centre, 171 Tottenham Court Road, London, W.1. (Personal communication)

29. Dybowski, W. and Franklin, D.A. (1964)
The Computer-Assisted Identification of Bacteria from Observations and Tests.
Report to Elliott Medical Automation Ltd., 69 Chenies Mews, London.

30./

30. Tsumoto, T.T., (1958)
The I.B.M. Taxonomy Application M and A-6, part XII, p 30.
Program Information Department, I.B.M. Data Processing Division,
112 E. Post Road, White Plains, New York, U.S.A.

31. Overall, J.E. and Williams, C.M. (1961)
Proc. 3rd International Conf. on Med. Electronics.
Vol. 3 247, Iliffe, London.

32. Brit. med. J. (1964), 1, 1266

33. Engle, R.L. (1963) Arch. Intern. Med. 112, 530

34. Nugent, C.A., Warner, H.R., Dunn, J.T. and Tyler, F.H. (1964)
J. clin. Endocr. 24, 621

35. Mooney, H.J. (1956)
Facts from Figures, 3rd ed. Penguin Books, London. p.246

36. Bancroft, J.N. (1962)
J. roy. statist. Soc. B. 24, 251

37. Goodman, L.A. (1963)
J. roy. statist. Soc. A. 126, 94

38. Dingmore, R.S. and Hazard, J.B. (1948)
Cleveland clin. Quart. 15, 104

39. Gallo, G. Jr. (1950)
J. Amer. med. Ass. 142, 450

40. Murray, I.P.C. (1964) Thyroid Disorders: A Guide to
Diagnosis and Treatment, Pitman Medical Publishing Co.
Ltd., London.

41. Lindsay, S., (1964)
In The Thyroid Gland. Ed. R. Pitt-Rivers and W.R., Trotter.
Butterworth, London. p.223.

42. Sokal, J.E. (1954a)
J. Amer. med. Ass. 154, 1321

43. Sokal, J.E. (1954b)
Surg. Gynec. Obstet. 99, 103

PART 1

SECTION 2

TABLES AND APPENDIX

Table 1

Average plasma radioactivity from 35 to 180 min. following intravenous injection of radioiodine in 6 patients.

Table I.

Values expressed as per cent dose per 100 ml. plasma

* Values obtained by integration	* Values obtained by substitution at 77 min.
0.60	0.56
0.33	0.29
0.30	0.25
0.30	0.27
0.24	0.18
0.50	0.50

* For explanation of this procedure see text

Correlation coefficient of these values = 0.99

Difference between means not significant

($t = 0.32$ $0.9 > P < 0.8$)

Table 2

A comparison of PII values given by the I/Cr ratio technique with those given by an isotope dilution method.

Table 2

± Standard deviation

Condition	No. of Patients	Mean PII (ug per cent)	
		I/Cx Ratio Technique	Isotope Dilution Method
Euthyroid	31	0.31	0.32
		± 0.24	± 0.22
Simple Goitre	16	0.10	0.16
		± 0.096	± 0.096
Thyrotoxicosis	9	0.19	0.17
		± 0.065	± 0.04

I/Cx ratio technique

Thyrotoxicosis v. euthyroid $t = 1.4$ 0.2 P 0.1
Simple Goitre v. euthyroid $t = 2.11$ P 0.05

Isotope dilution method

Simple Goitre v. euthyroid $t = 2.73$ P 0.01

Table 3

Mean PBI levels obtained by various workers in euthyroid subjects. Numbers in column 1 give references to these papers.

Table 3

Ranges shown in parentheses. Standard deviation is also shown (±). All results obtained by an isotope dilution technique.

Authors		Year	PII (ug. per cent)
Stanley	(1)	1949	"up to 1 mg. usually less"
Perry and Hughes	(3)	1952	0.17 ± 0.05
Zingg and Perry	(4)	1953	0.24 ± 0.04
Reilly et al	(5)	1958	0.55 ± 0.06
Feinberg et al	(6)	1959	0.25 ± 0.06
Fitting	(7)	1960	0.14 (0.015 to 0.375)
Alexander et al	(11)	1962	0.19 ± 0.115 (0.04 to 0.57)
de Crombrugge et al	(9)	1963	0.14 ± 0.055 (0.05 - 0.26)
Aboul-Khair	(8)	1965	0.2 ± 0.07

Appendix A

Individual PEI values (ug per cent) obtained for each subject by an isotope dilution technique and by the I/Cr ratio technique.

Appendix A

RAW DATA

Isotope Dilution Technique	K/Ca Ratio Technique	Isotope Dilution Technique	K/Ca Ratio Technique
0.10	0.14	0.29	0.28
0.12	0.06	0.23	0.33
0.12	0.12	0.24	0.30
0.11	0.10	0.25	0.32
0.12	0.10	0.26	0.32
0.13	0.11	0.30	0.31
0.16	0.13	0.32	0.39
0.18	0.13	0.35	0.42
0.20	0.13	0.36	0.43
0.22	0.17	0.40	0.43
0.22	0.20	0.40	0.19
0.23	0.19	0.32	0.29
0.23	0.22	0.48	0.47

Appendix A (continued)

Isotope Dilution Technique	I/Cr Ratio Technique	Isotope Dilution Technique	I/Cr Ratio Technique
0.32	0.26	1.02	1.00
0.52	0.34	1.03	1.10
0.55	0.56		

PATIENTS WITH SIMPLE GOITRE

0.08	0.05	0.08	0.17
0.06	0.07	0.12	0.10
0.08	0.10	0.17	0.35
0.09	0.11	0.20	0.13
0.11	0.14	0.28	0.32
0.12	0.14	0.40	0.21
0.12	0.15	0.30	0.33
0.10	0.17	0.18	0.29

Appendix A (continued)

PHANTOMIC PATIENTS

Isotope Dilution Technique	I/Cr Ratio Technique	Isotope Dilution Technique	I/Cr Ratio Technique
0.10	0.12	0.19	0.20
0.12	0.12	0.17	0.14
0.20	0.20	0.22	0.25
0.18	0.22	0.14	0.13
0.20	0.22		

PART 1

SECTION 3

TABLES AND APPENDIX

Table 1

Details of the 174 pairs of twins assessed for politics.

Table 1

Twin Category	No. of Pairs	Mean Age (years)	Age Range (years)	No. of Pairs Separated *
Dizygotic female	53	21.2	12-66	10
Monozygotic female	28	22.1	12-70	8
Dizygotic male	22	23.9	12-65	4
Monozygotic male	20	21.7	12-47	4
Monozygotic male + female	51	20.6	12-64	16

* living apart for 1 year or longer

Table 2

Number of individuals from 174 twin pairs examined subdivided according to age, sex and presence or absence of goitre.

Table 2

Age Range (years)	Females			Males		
	Non-Goitrous	Goitrous	Per Cent Goitrous	Non-Goitrous	Goitrous	Per Cent Goitrous
12–15	69	38	33	65	1	1
16–20	31	21	40	20	8	29
21–30	17	13	43	12	2	14
> 30	25	9	26	23	3	12
> 12	138	75	35	121	14	10

Table 3

Details of the 120 twin pairs in whom plasma inorganic iodine was measured.

Table 3

Twin Category	No. of Pairs	Mean Age (years)	Age Range (years)	No. of Pairs Separated *
Monozygotic female	39	22.2	12-66	9
Dizygotic female	24	23.0	12-79	7
Monozygotic male	16	21.6	12-39	4
Dizygotic male	7	23.7	14-46	1
Dizygotic male + female	34	24.5	12-64	13

* Living apart for 1 year or longer

Table 4

Number of individuals from 120 twin pairs in whom PBI was measured subdivided according to age, sex and presence or absence of goitre.

Table 4

Age Range (years)	Females			Male		
	Non-Coitarche	Coitarche	Per Cent Coitarche	Non-Coitarche	Coitarche	Per Cent Coitarche
12-15	40	20	33	34	0	0
16-20	29	15	34	15	5	25
21-30	15	11	42	10	2	17
30	24	6	17	13	1	7
12	108	52	33	72	8	10

Table 5

Percentage concealment votes for Gaitho

in 174 both polls.

Table 5

* Both tubes patterns

† Both tubes non-patterns

Numbers in brackets refer to number of twin pairs rather than percentages

		Positive Concordance *	Negative Concordance †	Discordance
Monozygotic females	(53)	28.3 (15)	56.6 (30)	15.1 (8)
Dizygotic females	(28)	25.0 (7)	46.4 (13)	28.6 (8)
Monozygotic males	(22)	9.1 (2)	81.8 (18)	9.1 (2)
Dizygotic males	(20)	0.0 (0)	85.0 (17)	15.0 (3)
Dizygotic males + females	(51)	5.9 (3)	66.7 (34)	27.4 (14)

Table 6

The likelihood for each of the 121 combinations of h and x calculated from the equation $L = K\,(x + h - hx)^{45}\,[(1 - x)\,(1 - h)]^{9}\,x^{20}\,(1 - x)^{0}$. For full explanation see text.

Table 6

Only the relative magnitudes of likelihood are relevant, hence the factor K has been omitted and the uniform *a priori* distribution has been taken to be 1 for all h_i s' pairs

h \ s	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	Total
0.0							2	367	3293	105		3767
0.1							13	1043	5411	73		6544
0.2							77	2491	4969	48		7595
0.3						3	344	4879	4912	27		10165
0.4						25	1144	9598	4037	13		14817
0.5						136	2691	8925	2554	5		14311
0.6					9	416	4047	7160	1163	1		12796
0.7					27	637	3288	3217	306			7475
0.8					25	324	949	542	31			1970
0.9					2	14	25	9				50
1.0												0

Table 7

Nine subjects whose PEI values were not included in the analysis.

Table 7

PBI (ug. per cent)	Age (years)	Sex	Condition
1.21	54	Male	Non-goitrous
1.32	16	Female	Goitrous
27.43	13	Female	Non-goitrous
1.08	33	Female	Non-goitrous
1.88	14	Male	Non-goitrous
1.26	17	Female	Non-goitrous
2.26	17	Female	Non-goitrous
1.54	49	Female	Non-goitrous
4.50	23	Female	Goitrous

Table 8

Mean values for PII levels (± standard deviation) in goitrous and non-goitrous individuals. PII expressed as ug per cent.

Table 8

	Non-Coltrane		Coltrane		
Sex	No.	PII	No.	PII	Differences
Female	103	0.24 ± 0.179	59	0.21 ± 0.099	Not significant
Male	79	0.21 ± 0.142	8	0.32 ± 0.282	Not significant
Differences:		Not significant		Not significant	

Note: calculations were made using 253 of the 249 individuals in Table 4. The PII values > 2.0 sg. per cent were omitted from the analysis.

Table 9

Mean PII values (± standard deviation) according to sex, age and goitre status.

Table 9

PII expressed as ug per dsA. Figures in brackets refer to the number of individuals in that category.

Age Range (years)	Females		Males	
	Non-Goitrous	Goitrous	Non-Goitrous	Goitrous
12-15	0.16 ± 0.035 (38)	0.19 ± 0.101 (20)	0.19 ± 0.100 (33)	-
16-20	0.25 ± 0.200 (27)	0.25 ± 0.172 (14)	0.22 ± 0.145 (15)	0.39 ± 0.322 (5)
21-30	0.29 ± 0.224 (15)	0.24 ± 0.124 (10)	0.17 ± 0.075 (10)	0.09 (2)
30	0.30 ± 0.215 (23)	0.31 ± 0.246 (6)	0.29 ± 0.257 (12)	0.41 (1)
15	0.29 ± 0.206 (65)	0.23 ± 0.099 (30)	0.23 ± 0.197 (37)	0.32 ± 0.282 (6)

Appendix A

Plasma fibrinogen levels (mg per cent) pre, post and hypocalcemia plasma for each individual in the study. Coiled stalks is also shown

Appendix A

* + = visible and palpable thyroid enlargement was present

† H = Homozygous B = Biygous /

Cobbre *	Sex	PII (ug per cent)	Zygosity Class †	Age (years)
-	Male	0.44	B	13
-	Female	0.57	B	19
-	Male	0.12	H	30
+	Male	0.12	H	30
+	Female	0.12	B	12
-	Female	0.13	B	12

Appendix A (continued)

Cetacean *	Sex	PCB (µg per gm)	Zygosity Class †	Age (years)
"	Female	"	2	14
"	Male	"	2	14
"	Female	"	3	11
"	Male	"	3	12
"	Female	"	3	13
"	Male	"	3	14
"	Female	0.14	2	12
"	Female	0.21	3	12
"	Female	0.22	2	13
"	Female	0.14	1	13

Appendix A (continued)

Solano *	Sex	PTT (us sec cm^{-1})	Dyspnea*	Age (years)
+	Male	0.80	+	18
+	Female	0.89	+	19
-	Female	-	-	21
-	Female	-	-	21
+	Male	0.80	+	25
+	Female	0.85	+	25
-	Female	-	-	22
-	Male	-	-	22
+	Female	0.81	+	22
+	Female	0.78	+	17

Appendix A (continued)

Coltre [*]	Sex	PIT (ng per seal)	Severity Class [†]	Age (years)
-	Female	0.15	3	15
-	Female	0.16	3	15
-	Female	-	3	15
-	Female	-	3	13
-	Male	0.20	3	15
-	Male	0.08	3	16
-	Male	1.02	3	54
-	Male	0.42	3	54
+	Female	0.17	3	25
+	Female	0.13	3	26

Appendix A (continued)

Codine *	Sex	PII (ug per cent)	Zygosity Class †	Age (years)
-	Male	-	M	40
-	Male	-	M	48
+	Female	0.14	D	14
-	Male	0.23	D	14
-	Female	-	S	13
-	Male	-	S	13
-	Female	-	D	15
-	Male	-	D	15
-	Female	-	M	12
-	Female	-	M	12

Appendix A (continued)

Retino *	Sex	FII (sc per cent)	Zygosity Class †	Age (years)
-	Female	0.39	3	17
-	Male	0.29	3	17
+	Female	1.32	1	16
+	Female	0.52	1	16
+	Female	-	2	29
+	Female	-	2	29
-	Male	0.23	3	13
-	Female	0.19	3	13
+	Female	-	3	14
-	Male	-	3	14

Appendix 1 (continued)

Goitre *	Sex	TSI (ug per cent)	Rigosity Class †	Age (years)
-	Female	0.08	1	14
-	Female	0.07	1	14
+	Male	0.17	2	19
+	Female	0.09	2	19
+	Female	0.16	1	22
+	Female	0.13	1	22
-	Male	-	0	14
+	Female	-	2	14
-	Male	0.09	2	27
+	Female	0.02	0	27

Appendix A (continued)

	Goitre *	Sex	PBI (ug per cent)	Hypothy Class †	Age (years)
	-	Female	0.11	D	14
	-	Female	0.04	D	14
	-	Female	27.42	D	13
	-	Female	1.08	D	13
	-	Male	-	D	47
	-	Male	-	D	47
	-	Male	0.25	D	16
	-	Female	0.21	D	16
	-	Male	-	D	15
	-	Male	-	D	15

Appendix A (continued)

Quitze *	Sex	PTI (ug per cent)	Zygosity Class †	Age (years)
-	Female	0.10	D	12
-	Female	0.40	D	22
-	Male	0.38	D	14
-	Female	0.41	D	14
-	Female	0.66	D	17
-	Female	0.16	D	17
-	Male	-	D	13
-	Male	-	D	13
-	Male	0.23	M	15
-	Male	0.13	M	15
-	Male	0.11	D	17
-	Male	0.13	D	17

Appendix A (continued)

Patient *	Sex	PII (µg per cent)	Toxicity Class †	Age (years)
-	Male	0.11	3	13
-	Female	0.09	3	13
-	Male	0.11	3	14
-	Male	0.09	3	14
-	Female	-	3	14
-	Male	-	3	14
-	Male	0.46	3	18
+	Female	0.25	3	18
+	Female	0.34	3	16
+	Female	0.34	3	16
-	Female	0.18	3	50
-	Female	0.07	3	50

Appendix A (continued)

Goitre *	Sex	PII (µg per cent)	Zygosity Class †	Age (years)
-	Female	0.09	M	14
-	Female	0.06	M	14
+	Female	0.28	M	12
+	Female	0.44	M	12
+	Female	0.12	M	13
+	Female	0.13	M	13
-	Male	-	D	14
-	Male	-	D	14
-	Male	0.53	M	14
-	Male	1.88	M	14
-	Male	-	D	14
-	Female	-	D	14

Appendix A (continued)

Centre *	Sex	PII (µg per cent)	Opacity Class †	Age (years)
-	Male	0.30	2	64
-	Female	0.16	2	64
-	Male	0.11	2	14
-	Male	0.09	2	14
-	Female	0.07	2	78
+	Female	0.22	2	70
-	Female	-	2	12
+	Female	-	2	12
-	Female	0.63	2	67
-	Female	0.24	2	27
-	Male	0.37	2	13
-	Female	0.31	2	13

Appendix A (continued)

Goiter *	Sex	PTI (mg per cent)	Obesity class †	Age (years)
-	Female	-	N	14
-	Female	-	N	14
-	Female	-	O	12
-	Female	-	O	12
-	Male	0.13	O	16
+	Male	0.07	O	16
-	Male	-	N	16
-	Male	-	N	16
-	Female	0.15	N	25
-	Female	0.17	N	25

Appendix A (continued)

Goitre *	Sex	PII (µg per cent)	Zygosity Class †	Age (years)
-	Female	0.30	D	55
-	Male	0.18	D	55
+	Female	0.31	M	20
+	Female	0.35	M	20
+	Female	-	M	49
+	Female	-	M	49
+	Male	-	D	15
+	Female	-	D	15
-	Male	-	D	13
-	Male	-	D	13
-	Male	0.51	D	17
-	Male	0.12	D	17

Appendix A (continued)

Coitus *	Sex	PII (µg per cent)	Zygosity Class †	Age (years)
-	Male	0.27	M	13
-	Male	0.21	M	13
-	Female	0.22	M	16
-	Female	0.25	M	16
-	Female	0.35	M	34
-	Female	0.53	M	34
-	Female	0.91	M	39
-	Female	0.17	M	39
-	Male	-	M	13
-	Male	-	M	13
-	Female	0.15	D	16
-	Female	0.20	D	16

Appendix A (continued)

Goitre *	Sex	PBI (ug per cent)	Zygosity Class †	Age (years)
+	Female	-	M	13
+	Female	-	M	13
-	Male	0.70	D	46
-	Male	0.93	D	45
-	Female	-	M	32
+	Female	-	M	32
-	Female	0.78	M	26
+	Female	0.45	M	26
+	Female	0.12	D	13
-	Female	0.11	D	13
-	Male	-	D	13
-	Male	-	D	13

Appendix 1 (continued)

Colony *		Sex	PRT (as log cm²)	Sporozoite Gloss +	Age (years)
■	■	Male	0.25	5	33
+	+	Female	0.52	5	33
■	■	Female	0.61	6	33
■	■	Female	0.25	6	33
■	+	Female	.	M	35
+	+	Female	.	M	35
+	+	Female	.	M	35
+	+	Female	.	M	35
+	+	Female	0.34	6	35
+	+	Female	0.15	6	35

Appendix 4 (continued)

Goitre *	Sex	PBI (µg per cent)	Dysgenic Class †	Age (years)
-	Male	0.21	N	30
-	Male	0.31	N	39
-	Male	-	D	22
-	Male	-	D	22
+	Female	0.15	N	17
-	Female	0.18	N	17
-	Female	0.28	N	66
-	Female	0.69	N	66
+	Female	-	D	14
-	Male	-	D	14
+	Female	0.13	N	12
+	Female	0.16	N	12

Appendix 1 (continued)

Culture *	Sex	PII (as per cent)	Zygosity Class †	Age (years)
-	Female	1.25	M	17
-	Female	0.74	M	17
-	Female	0.13	M	22
-	Female	0.19	M	22
-	Male	0.15	D	16
-	Female	0.11	D	16
+	Male	0.33	M	19
+	Male	0.69	M	19
-	Male	-	D	12
-	Male	-	D	12
-	Female	2.26	M	17
-	Female	0.15	M	17

Appendix 3 (continued)

Cadaver *	Sex	PH (µg per cent)	Hygadig Class †	Age (years)
0	Female	-	M	12
0	Female	-	M	12
0	Male	-	M	17
0	Male	-	M	17
0	Male	0.13	M	14
0	Male	0.22	M	14
0	Female	-	M	13
0	Female	-	M	13
0	Male	0.08	M	16
0	Male	0.08	M	16
0	Female	0.25	M	13
0	Female	0.24	M	13

Age

Appendix 4 (continued)

Code	Sex	PAS (ug per cm²)	Capsaicin	Stage	Age (years)
0	Female	0	N	+	29
0	Female	0	N		33
0	Male	0	N	+	65
0	Male	0	N		65
+	Female	0	S	+	34
+	Female	0	S		34
0	Female	0	N	+	25
0	Female	0	N		25
0	Female	0.05	N	+	55
0	Female	0.05	N		55
0	Male	0.18	S	+	24
0	Male	0.23	S		24

Appendix A (continued)

Isolate *	Sex	WT (to the sea)	Spent by mass †	Age (years)
◆ ◆	Female	0.49	■ ■	12
	Female	0.58	■ ■	12
◆ ◆	Female	0.22	■ ■	13
	Male	0.60	■ ■	13
◆ ◆	Female	.	■ ■	14
	Male	.	■ ■	14
◆ ◆	Male	.	■ ■	22
	Male	.	■ ■	22
◆ ◆	Male	0.15	■ ■	23
	Male	0.39	■ ■	23
◆ ◆	Female	0.68	■ ■	28
	Female	0.35	■ ■	28

Appendix A (continued)

Colour *	Sex	PAH (ug per cent)	Zygosity Class †	Age (years)
● ○	Male	0.32	H	13
● ○	Male	0.37	H	13
◆	Female	0.39	D	32
◆	Female	0.26	D	32
○ ○	Male	-	D	15
○	Female	-	D	15
● ●	Female	0.11	H	13
●	Female	0.31	H	13
● ●	Female	0.44	H	50
●	Female	0.28	H	50
○ ○	Male	0.13	H	12
○	Male	0.07	H	12

Appendix A (continued)

Codon *	Sex	PTC (mg per cent)	Zygosity Class †	Age (years)
-	Male	0.27	D	12
-	Female	0.08	D	12
+	Female	-	H	20
+	Female	-	H	20
+	Female	0.08	H	14
+	Female	0.14	H	14
-	Male	-	D	16
-	Male	-	D	16
-	Male	-	D	13
-	Male	-	D	13
-	Male	-	D	14
-	Female	-	D	14

Appendix A (continued)

Goitre *	Sex	TBI (ug per cent)	Exposure class †	Age (years)
+	Male	-	D	37
-	Male	-	D	37
-	Female	0.11	M	16
-	Female	0.09	M	16
-	Female	1.54	D	49
+	Female	0.77	D	49
-	Male	0.44	D	33
-	Female	0.12	D	33
-	Female	-	D	15
-	Male	-	D	15
-	Female	0.10	D	14
-	Male	0.17	D	14

Appendix A (continued)

Goitre *	Sex	PBI (µg per cent)	Symptomatology Class †	Age (years)
-	Male	0.13	D	28
+	Female	0.17	D	28
-	Female	0.09	M	15
-	Female	0.21	M	15
+	Female	0.26	D	15
+	Female	0.32	D	15
-	Male	-	D	42
-	Male	-	D	42
-	Female	0.17	D	11
-	Male	0.15	D	11
-	Male	0.11	D	15
-	Male	0.11	D	15

Appendix A (continued)

Twin *	Sex	PTC (log per cent)	Zygosity Class †	Age (years)
+	Female	0.23	M	17
+	Female	0.11	M	17
+	Male	-	D	13
+	Female	-	D	13
+	Female	0.19	D	12
+	Female	0.26	D	12
+	Female	0.23	D	18
+	Female	0.14	D	18
+	Male	-	M	18
+	Male	-	M	18
+	Female	0.15	M	22
+	Female	0.09	M	22

Appendix A (continued)

Coitus *	Sex	PII (µg per cent)	Zygosity Class †	Age (years)
o	Female	0.11	M	16
o	Female	0.12	M	18
o	Female	0.16	D	25
o	Female	0.37	D	25
o	Male	0.02	M	39
o	Male	0.14	M	39
+	Female	0.06	D	27
+	Female	0.05	D	27
o	Female	0.05	D	14
o	Male	0.04	D	14
o	Female	0.25	D	21
o	Male	0.10	D	21

Appendix A (continued)

Co-twins	Sex	PTI (as per cent)	Zygosity	Class	Age (years)
0 0	Female Female	0.22 0.25	D D	I I	31 31
0 +	Male Female	0.24 4.50	D D	II II	33 33
+ 0	Female Female	0.15 0.29	M M	II II	30 30
+ 0	Female Female	0.37 0.19	D D	II II	42 42
0 0	Female Female	0.16 0.11	M M	II II	19 19
0 0	Female Female	0.55 0.24	M M	II II	62 62

Appendix A (continued)

Co-ded as	Sex	SAI (as per cent)	Agreement	Age (years)
+ +	Female	0.57	+	44
	Male	0.62	+	44
+ +	Female	0.63	+	33
	Male	0.05	-	33
+ +	Female	0.33	+	30
	Female	0.55	+	30
+ +	Male	0.07	-	40
	Female	0.24	+	40
+ +	Male	0.19	-	21
	Male	0.21	+	21
+ +	Female	0.50	+	55
	Male	0.08	-	55

Appendix A (continued)

Colony [a]	Sex	PCB (µg per cell)	Bycosity Class [†]	Age (years)
4	Male	0.41	D	32
2	Female	0.65	D	31
6	Male	0.19	C	62
5	Female	0.13	C	61
9	Male	0.23	D	28
8	Female	0.07	B	26
6	Female	0.39	D	12
4	Female	0.17	B	13
6	Female	0.21	D	12
6	Female	0.15	D	12
8	Female	0.13	D	30
8	Male	0.08	D	30

PART 2

SECTION 1

TABLES AND APPENDICES

Table 1

Mean thyroidal ^{131}I uptake at 24 hours in a variety of thyroid states before and after 2 mg KI given with the second ^{131}I tracer dose.

Table 1

The number of patients with inhibition of uptake > 55% each group is shown. Standard deviation is also shown (±)

Group	Condition	No. of cases	Mean Thyroidal ^{131}I uptake				No. with % inhibition of uptake > 55%
			Initial	Final	Change	% Inhibition	
A	Controls	11	48	39	14	25	0/11
			±12.9	±12.1		±23.7	
B	Hashimoto's disease	25	49	32	57	75	20/25
			±10.5	±5.3		±10.6	
C	Simple goitre	22	57	49	8	34	0/22
			±15.6	±16.2		±25.3	

Table 1 (continued)

	Condition	No. of cases	Mean thyroidal ^{131}I uptake				No. with % inhibition of uptake > 55%
			Initial	Final	Change	% Inhibition	
D	Thyroidectomy for simple goitre	5	42 ±10.4	17 ±7.6	25	60 ±11.4	4/5
E	Thyrotoxicosis	11	79 ±14.8	48 ±22.2	31	39 ±22.1	2/11
F	Thyroidectomy for thyrotoxicosis	13	47 ±18.8	4 ±4.4	43	88 ±10.1	13/13
G	Radioiodine for thyrotoxicosis	23	49 ±14.4	12 ±12.3	37	75 ±21.6	19/23

Table 1 (continued)

	Condition	No. of cases	Mean Thyroidal ^{131}I uptake				No. with % inhibition of uptake > 5%
			Initial	Final	Change	% Inhibition	
E	Pendred's Syndrome	1	54	37	17	31	0/1

% Inhibition

Av. B t = 7.7 p < 0.0001
Av. C t = 1.4 not significant
Av. D t = 5.4 p < 0.0001
Av. E t = 1.2 p not significant
Av. F t = 17.5 p < 0.0001
Av. G t = 5.6 p < 0.0001

Table 2

Mean plasma $PB^{131}I$ levels in a variety of thyroid states before and after 2 mg KI given with the second ^{131}I tracer dose.

Table 2

The number of patients with inhibition of $PB^{131}I$ > 5% in each group is shown. Standard deviation is also shown (±)

In controls, patients with simple goitre, patients thyroidectomised for non-toxic goitre and patients treated by Carbimazole for thyrotoxicosis $PB^{131}I$ values recorded before RI were too small to allow valid manipulation.

Condition	No. of cases	Mean 48 hour plasma $PB^{131}I$ level: Initial	Final	Change	% Inhibition	No. with % inhibition of $PB^{131}I$ > 5%
Thyrotoxicosis	11	1.64 ±1.16	0.58 ±0.62	1.05	64 ±28.2	7/11
Thyroidectomy for thyrotoxicosis	13	0.50 ±0.34	0.34 ± 0.20	0.16	27 ±37.8	3/13

Table 2 (continued)

Condition	No. of cases	Mean 48 hour plasma $PB^{131}I$ level				No. with % inhibition of $PB^{131}I$ > 55%
		Initial	Final	Change	% Inhibition	
Radioiodine for thyrotoxicosis	23	0.57 ±0.32	0.19 ±0.36	0.78	79 ±18.9	22/23
Hashimoto's disease	25	0.69 ±0.47	0.25 ±0.30	0.44	54 ±41	15/25
Pendred's Syndrome	1	0.31	0.21	0.10	32	0/1

Appendix A

Values for 24 hour thyroidal ^{131}I uptakes and 40 hour plasma PB ^{131}I levels for the individual patients in this study before ("Initial") and after ("Final") the addition of 2 mg KI to the oral ^{131}I.

Appendix A

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
			control subjects				
60	37	23	46	0.00	0.00	0.00	0
37	52	+15	+41	0.00	0.00	0.00	0
53	39	14	27	0.00	0.00	0.00	0
22	17	5	23	0.00	0.00	0.00	0
52	26	26	50	0.00	0.00	0.00	0
62	57	5	8	0.00	0.00	0.00	0

Appendix A (continued)

	24 hour thyroidal ^{131}I uptake (% dose)			48 hour plasma PB ^{131}I level (% dose / l. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
46	29	17	39	0.00	0.00	0.00	0
53	34	19	36	0.00	0.00	0.00	0
54	24	30	55	0.00	0.00	0.00	0
36	38	+ 2	+ 6	0.00	0.00	0.00	0
43	25	18	42	0.00	0.00	0.00	0

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
PATIENTS WITH HASHIMOTO'S DISEASE							
53	12	41	77	1.00	0.46	0.54	54
32	8	24	75	1.09	0.31	0.78	72
56	10	46	82	1.16	0.15	1.01	87
50	7	43	86	0.30	0.00	0.30	100
69	15	54	78	0.00	0.00	0.00	0
40	2	38	95	0.38	0.00	0.38	100

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
39	17	22	56	0.53	0.21	0.32	60
45	18	27	60	0.61	0.54	0.07	10
63	15	48	76	0.43	0.21	0.22	51
40	15	25	63	0.33	0.19	0.14	42
43	6	37	86	0.89	0.23	0.66	74
53	16	37	70	1.08	0.35	0.73	68
33	7	26	79	0.48	0.11	0.37	77
50	40	10	80	1.20	0.63	0.57	48

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
36	6	30	83	0.88	0.13	0.75	85
59	15	43	74	1.18	0.34	0.84	71
45	16	29	64	0.51	0.00	0.51	100
63	19	44	70	0.35	0.08	0.27	77
35	3	32	92	0.35	0.35	0.00	100
48	23	25	52	0.59	0.30	0.28	48
38	8	30	79	0.67	0.56	0.11	16
67	12	55	82	0.47	0.28	0.19	40

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / l. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
46	11	29	73	0.30	0.26	0.34	47
46	8	38	82	1.09	0.33	0.76	70
49	17	32	66	1.33	0.55	0.78	59
			PATIENTS WITH SIMPLE GOITRE				
55	40	15	27	0.00	0.00	0.00	0
48	27	21	44	0.00	0.00	0.00	0
54	44	10	19	0.00	0.00	0.00	0

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
46	37	9	20	0.00	0.00	0.00	0
49	28	21	43	0.00	0.00	0.00	0
35	49	+14	+40	0.00	0.00	0.00	0
55	48	7	13	0.00	0.00	0.00	0
59	45	14	24	0.00	0.00	0.00	0
78	64	14	18	0.00	0.00	0.00	0
36	41	+ 5	+14	0.00	0.00	0.00	0
69	48	21	30	0.00	0.00	0.00	0

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
44	37	7	16	0.00	0.00	0.00	0
68	32	36	53	0.00	0.00	0.00	0
36	45	+ 9	+25	0.00	0.00	0.00	0
56	65	+ 9	+16	0.00	0.00	0.00	0
88	64	24	27	0.00	0.00	0.00	0
58	60	+ 2	+ 3	0.00	0.00	0.00	0
54	50	4	7	0.00	0.00	0.00	0
49	59	+10	+20	0.00	0.00	0.00	0

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				24 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
95	100	+ 5	+ 5	0.00	0.00	0.00	0
70	35	36	51	0.00	0.00	0.00	0
62	62	0	0	0.00	0.00	0.00	0
			REMOTELY PATIENTS				
54	37	17	32	3.40	0.00	3.40	100
78	55	23	30	3.04	1.96	1.08	36
88	68	20	23	0.27	0.00	0.27	100

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
67	66	21	24	1.42	1.16	0.26	18
100	94	6	6	0.73	0.49	0.24	33
92	48	44	48	0.77	0.27	0.50	65
100	55	45	45	2.05	0.51	1.54	75
65	10	55	85	1.11	0.26	0.85	75
68	48	20	29	0.35	0.22	0.13	37
77	18	59	77	1.59	0.22	1.37	86
60	42	18	30	3.31	1.25	2.06	62

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
PATIENTS RECEIVED AFTER ^{131}I THERAPY FOR HYPERTHYROIDISM							
52	10	42	81	1.27	0.37	0.90	71
62	40	22	35	0.48	0.33	0.15	31
36	29	7	19	1.07	0.38	0.69	63
47	31	16	34	0.79	0.07	0.72	91
68	4	70	95	1.47	0.04	1.43	97
59	6	53	90	0.99	0.17	0.82	83

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / l. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
39	6	33	85	0.94	0.37	0.57	62
42	16	26	62	0.63	0.22	0.41	65
45	3	42	93	1.09	0.14	0.95	87
51	20	31	62	2.14	0.30	1.84	86
26	6	20	77	0.45	0.00	0.45	100
49	8	41	84	0.71	0.23	0.48	68
39	3	36	92	0.61	0.09	0.52	85
54	15	39	72	2.49	0.36	2.12	85

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
60	2	58	97	0.52	0.05	0.53	91
32	4	28	88	0.32	0.00	0.32	100
39	8	31	79	0.35	0.23	0.67	73
37	5	32	86	0.32	0.00	0.32	100
33	4	29	88	0.88	0.12	0.76	86
61	32	49	80	1.63	0.32	1.27	78
57	4	53	93	0.37	0.11	0.26	70
40	7	33	83	1.73	0.28	1.45	84

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
91	45	46	50	0.63	0.42	0.21	33
PATIENTS EUTHYROID AFTER THYROIDECTOMY FOR THYROTOXICOSIS							
80	1	79	100	1.03	0.72	0.31	30
72	3	69	96	0.61	0.35	0.26	42
76	14	64	82	0.59	0.54	0.05	9
25	4	21	84	0.67	0.35	0.42	63

Appendix A (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / l. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
56	1	55	98	0.42	0.21	0.21	50
41	13	28	68	0.45	0.42	0.03	7
37	2	35	95	0.27	0.24	0.03	11
36	2	34	94	0.39	0.29	0.10	26
41	6	35	85	0.16	0.24	+0.08	+50
43	2	41	95	1.11	0.48	0.63	56
35	10	25	71	0.08	0.08	0.00	0
33	6	27	82	0.15	0.18	+0.03	+20

Appendix 1 (continued)

24 hour thyroidal ^{131}I uptake (% dose)				48 hour plasma PB ^{131}I level (% dose / L. plasma)			
Initial	Final	Change	% Inhibition	Initial	Final	Change	% Inhibition
28	5	23	82	0.27	0.00	0.27	100
PATIENTS AFTER INTRODUCTION POT SIMPLE GOITER							
47	18	29	62	0.00	0.00	0.00	0
45	18	27	60	0.00	0.00	0.00	0
47	28	19	42	0.00	0.00	0.00	0
46	14	32	70	0.00	0.00	0.00	0
23	7	16	70	0.00	0.00	0.00	0

PART 2

SECTION 2

TABLES AND APPENDICES

Table 1

Mean thyroidal absolute iodine uptake (AIU) calculated over the 30 minute period following intravenous injection of the tracer dose before and after addition of 2 mg. KI to the radioiodine.

Table 2

Standard deviation is shown (±). The individual values for the 2 patients with Hashimoto's disease are in brackets. The patients with Hashimoto's disease demonstrated greatest avidity for the RI load, followed by patients who had undergone thyroidectomy for thyrotoxicosis and patients with simple goitre. Radioiodine treated patients accumulated much less of the iodide load than did the other groups studied.

Condition	No. of patients	Mean ΔRU (μg/0.5 hr) Before RI	After RI
Thyroidectomy for thyrotoxicosis	6	1.14 ± 0.56	95 ± 70.2
Radioiodine for thyrotoxicosis	5	2.12 ± 0.74	23 ± 13.7
Hashimoto's disease	2	2.22 (1.88 - 2.55)	427 (422 - 432)
Simple goitre	5	3.63 ± 0.97	93 ± 29.8

Table 2

Results obtained by Pauls et al.

J. clin. Endocr. (1960) 20, 57.

Table 2

Results obtained by Pauls et al.

J. clin. Endocr. (1960) 20, 57.

Table 2

The 24 hour thyroidal ^{131}I uptake is lower in 3 patients with nodule goitre than the 6 hour uptake when 2 mg. KI is added to the tracer dose of ^{131}I. This situation does not pertain when the tracer dose is given alone.

Thyroidal ^{131}I uptake			
Before KI		After KI	
6 hour	24 hour	6 hour	24 hour
76	82	36	24
57	68	19	13
55	65	30	5

Appendix A

Individual values for thyroidal absolute iodine uptake (AIU) before and after addition of 2 mg. KI to the tracer dose of radioiodine for each patient studied.

Appendix A

Before RI			After RI
Plasma Inorganic Iodine (ug/100 ml)	Thyroid Radioiodine Plasma Clearance Rate (ml/min)	Absolute Iodine Uptake (ug/0.5 hr)	Absolute Iodine Uptake (ug/0.5 hr)
PATIENTS EUTHYROID AFTER THYROIDECTOMY FOR THYROTOXICOSIS			
0.10	30.0	0.90	38
0.12	25.0	0.90	52
0.13	29.3	0.91	113
0.05	40.7	0.61	244
0.20	22.5	1.35	90
0.26	37.7	2.16	75
PATIENTS EUTHYROID AFTER ^{131}I THERAPY FOR THYROTOXICOSIS			
0.10	40.7	1.2	33
0.29	32.0	2.0	6
0.15	33.7	1.5	11
0.22	33.0	2.2	33
0.10	53.3	2.9	33

Appendix A (continued)

	Before KI		After KI
Plasma Inorganic Iodine (ug/100 ml)	Thyroid Radioiodine Plasma Clearance Rate (ml/min)	Absolute Iodine Uptake (ug/0.5 hr)	Absolute Iodine Uptake (ug/0.5 hr)
	PATIENTS WITH SIMPLE GOITRE		
0.10	58.3	1.8	300
0.10	40.7	2.8	96
0.27	25.6	2.1	116
0.20	70.0	4.2	112
0.21	46.3	2.9	42
	PATIENTS WITH HASHIMOTO'S DISEASE		
0.30	20.9	1.80	402
0.21	40.1	2.55	432

PART 2

SECTION 3

TABLES AND APPENDIX

Table 1

Results of iodide inhibition tests and thyroid function tests in 10 patients who had received x-ray therapy for laryngeal cancer.

Table 1

Sex	Age	Dose of X-rays (rads)	Time after irradiation (years)	24 hour ^{131}I uptake Before RI	24 hour ^{131}I uptake After RI	Change	% Inhibition	Serum $PB^{127}I$ (µg %)
F	41	6000	2	25	16	9	36	5.7
F	51	5000	5	31	18	13	42	4.7
F	69	6000	2.5	45	33	12	27	4.4
F	46	5750	3	34	17	17	50	6.7
F	60	6000	2.5	19	17	2	12	8.6
F	66	5300	2.5	24	16	8	33	4.8

Table 1 (continued)

	Sex	Age	Dose of X-rays (rads)	Time after Irradiation (years)	24 hour ^{131}I uptake Before KI	24 hour ^{131}I uptake After KI	Change	% Inhibition	Serum PB^{127}I (µg %)
	F	66	6000	5.5	29	20	9	31	7.2
	M	68	6000	5.5	38	36	2	5	5.3
	M	50	5500	2	45	27	18	40	6.2
	F	70	6500	2	24	15	9	38	4.5
	Mean	57	5805	3.25	31.4	21.5	9.9	31	5.75

Table 2

Mean thyroidal ^{131}I uptake values at 24 hours when the tracer dose of ^{131}I is given with increasing doses of carrier iodide.

Table 2

(2 animals to each group). * mean of 4 animals

Gastrin added (ng)	24 hour thymidine (^{3}H) uptake (% dpm)	% inhibition of control uptake (16.6%)
0	16.6 *	0
1	15.7 *	6.5
4	17.0 *	+2.4
10	14.6	13.1
25	11.7	30.0
40	5.3	68.5
60	3.1	81.2

Table 3

Plan of experiment to measure thyroidal iodide trapping reserve in rats exposed to increasing doses of ^{131}I.

Table 3

^{131}I dose (uc)

		0	50	75
Group	Stable Iodide Added to Tracer Dose (ug)			
	0	5 rats	5 rats	5 rats
	10	5 rats	5 rats	5 rats
	20	5 rats	5 rats	5 rats
	40	5 rats	5 rats	5 rats

5 animals given 50 uc ^{131}I and 5 given 75 uc ^{131}I were used to measure background radioactivity

Table 4

Mean 24 hour ^{131}I uptake (per cent dose) by rat thyroid gland three weeks after irradiation by varying doses of ^{131}I, the tracer dose being administered with graded doses of ^{127}I carrier.

Table 4

The plan of this experiment is shown in Table 3.
Standard deviation (±)

		^{132}I dose µg		
		0	50	75
Carrier-free Iodide	0	32 ± 2.4	22 ± 3.3	15 ± 9.4
Added as	20	26 ± 3.2	16 ± 3.5	5 ± 5.3
Excess	20	7 ± 2.4	6 ± 2.6	3 ± 3.3
Dose (µg)	40	3 ± 1.8	5 ± 2.8	1 ± 1.3

Table 5

Mean Percent Inhibition of ^{131}I uptake by rat thyroid gland at 24 hours.

Table 5

The percent inhibition has been calculated by comparing the uptake of each rat to the mean uptake of the appropriate control group. Standard deviation (±). The results are expressed according to the plan given in Table 3.

		$^{131}I_2$ dose (µg)		
		0	50	75
Gastric Bolus Added to Tissue Dose (µg)	10	19 ± 9.8	49 ± 16.0	67 ± 24.6
	20	78 ± 6.9	75 ± 12.1	79 ± 21.2
	40	92 ± 4.6	75 ± 13.2	96 ± 8.8

Appendix A

Individual thyroid counts 24 hours after administration of the ^{131}I tracer dose with graded doses of carrier iodide.

Appendix A

Standard gave 526315 cp 60 sec.

		Carrier Iodide (ug)			
		0	10	20	40
Days	^{131}I (uc)				
	0	161290	151515	54945	4508
		208333	128205	33112	14577
		117647	155250	26925	28561
		153846	129870	25445	21786
		208333	121951	44642	2970
	50	131578	129870	67567	68606
		151515	91743	82967	68493
		169491	136986	42735	30838
		152515	109890	68111	69930
		126582	307527	51545	54945

Appendix A (continued)

	0	15	30	45
	120451	64935	57087	50335
	99029	128805	64935	52013
TS	212705	69945	49751	45918
	149853	78748	48850	45971
	185955	60240	58139	63965
75 ns ^{131}I to give background counts 3/52 later	37862	75 ns ^{131}I to give background counts three weeks later	49316	
	30664		60606	
	29239		58823	

Table 1

The probability matrix

Table 1

* The term "test" includes symptoms, clinical signs and the results of laboratory investigations.

† There were no patients with this disease who had this class of outcome for this test. This situation is represented by a small finite number rather than by zero because a zero in each of the three terms forming the denominator of expression (1) (see text) would cause this denominator to become zero and the result would be infinity which is unacceptable.

			Disease I		
			1	2	3
	Test *	Outcome E(j)	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
J1	Age (Years)	0-30	0.0370	0.2590	0.0850
		31-60	0.7360	0.6270	0.3930
		>60	0.2270	0.0590	0.5320

Table 1 (continued)

	Test*	Outcome I(J)	Disease I: 1 Hashimoto's Disease	2 Simple Goitre	3 Thyroid Cancer
J2	Clinical status	Hypothyroid	0.3208	0.0100†	0.0223
		Euthyroid	0.6626	0.9250	0.9677
		Hyperthyroid	0.0166	0.1650	0.0100
J3	Precipitin Test	+	0.7255	0.0010†	0.1033
		-	0.2745	0.9990	0.8967
J4	C.F. Test	++	0.6372	0.0100†	0.0200
		+	0.0698	0.0513	0.1601
		-	0.2930	0.9387	0.8719
J5	Serum globaline (G. per 100 ml.)	0-2.2	0.3404	0.8140	0.6296
		> 2.2	0.6595	0.1852	0.3704
J6	Gammaglobulin (G. per 100 ml.)	0-0.9	0.3314	0.9474	0.8667
		> 0.9	0.6686	0.0526	0.1333
J7	Thymol turbidity (Maclagan Units)	0-2.0	0.2553	0.8810	0.9677
		2.1-5	0.2766	0.1159	0.0323
		> 5	0.4681	0.0031†	0.0100†

Table 1 (continued)

	Test	Outcome K(j)	Disease I 1 Hashimoto's Disease	 2 Simple Goitre	 3 Thyroid Cancer
J8	Zinc sulphate turbidity (units)	5-12	0.2222	0.7222	0.7059
		13-25	0.6296	0.2578	0.2841
		>25	0.1482	0.0200†	0.0100†
J9	S.S.L. (cm. in 1 hr.)	0-20	0.4583	0.9998	0.5625
		21-40	0.3750	0.0001†	0.1563
		>40	0.1667	0.0001†	0.2812
J10	24 hour thyroidal ^{131}I uptake (per cent of dose)	0-30	0.0909	0.0833	0.3125
		31-60	0.7273	0.7500	0.5250
		>60	0.1818	0.1667	0.1625
J11	Duration (years)	0-1	0.3478	0.1667	0.4423
		1.1-10	0.5870	0.5208	0.4231
		>10	0.0652	0.3125	0.1346

Table 1 (continued)

			Disease I		
			1	2	3
	Test	Outcome K(j)	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
J12	Recent increase in size	No	0.3462	0.2000	0.8936
		Yes	0.6538	0.2000	0.1064
J13	Estimated size of gland (in Grms)	0-100	0.6226	0.8824	0.7083
		101-200	0.3019	0.0392	0.2500
		> 200	0.0755	0.0784	0.0417
J14	Nodular or diffuse	Nodular	0.5577	0.4706	0.7872
		Diffuse	0.4423	0.5294	0.2128
J15	Consistency	Firm	0.9057	0.5600	0.4500
		Hard	0.0566	0.0400	0.5300
		Soft	0.0377	0.4000	0.0200
J16	Discomfort	No	0.9434	0.6666	0.4545
		Yes	0.0566	0.3334	0.5455

Table 1 (continued)

	Test	Outcome E(J)	Disease I 1 Hashimoto's Disease	 2 Simple Goitre	 3 Thyroid Cancer
J17	Tracheal deviation or compression on x-ray	No	0.7703	0.8889	0.2083
		Yes	0.2500	0.1111	0.7917
J18	Laryngeal palsy	No	0.9900	0.9900	0.7647
		Yes	0.0100†	0.0100†	0.2353
J19	Fixation to tissues	No	0.9800	0.9020	0.3950
		Yes	0.0200	0.0980	0.6042
J20	Cervical lymph nodes	Impalpable	0.9811	0.9600	0.5510
		Palpable	0.0189	0.0400	0.4490
J21	P.B.^{127}I (ug per 100 ml.)	0-3	0.6316	0.0270	0.0769
		3.1-5	0.3421	0.4595	0.6923
		>5	0.0263	0.5135	0.2308

Table 1 (continued)

			Disease I		
			1	2	3
	Test	Outcome K(J)	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
J22	P.B.^{131}I at 48 hours (per cent of dose per litre of plasma)	0-0.2	0.2388	0.8095	0.6000
		0.21-1	0.3731	0.1895	0.3500
		>1	0.3881	0.0010†	0.0500
J23	^{131}I (expressed as percentage of ^{131}I)	0-79	0.6923	0.2000	0.9000
		>79	0.3077	0.8000	0.1000
J24	$KMnO_4$ discharge	+	0.6667	0.9134	0.9000
		-	0.3333	0.0866	0.1000
J25	Pyramidal lobe	Absent	0.8491	0.9608	0.9783
		Present	0.1509	0.0392	0.0217
J26	Pain in Goitre	No	0.9811	0.9348	0.6818
		Yes	0.0189	0.0652	0.3182

Table 1 (continued)

			Disease I		
			1	2	3
	Test	Outcome X(j)	Hashimoto's Disease	Simple Goiter	Thyroid Cancer
J27	Hoarseness	No	0.8654	0.9167	0.5933
		Yes	0.1346	0.0833	0.4167
J28	Dysphagia	No	0.8269	0.9375	0.7609
		Yes	0.1731	0.0625	0.2391
J29	Choking or tightness	No	0.7500	0.8125	0.4565
		Yes	0.2500	0.1875	0.5435
J30	Cough or wheeze	No	0.9608	0.9556	0.7234
		Yes	0.0392	0.0444	0.2766

Table 2

A hypothetical probability matrix showing two signs, one with two possible outcomes, the other with three possible outcomes.

Table 2

Test (T)	Result (KT)	Disease (X)		
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer
T_1	T_1X	$P_{T_1X\|h}$	$P_{T_1X\|s}$	$P_{T_1X\|c}$
	T_1Y	$P_{T_1Y\|h}$	$P_{T_1Y\|s}$	$P_{T_1Y\|c}$
T_2	T_2X	$P_{T_2X\|h}$	$P_{T_2X\|s}$	$P_{T_2X\|c}$
	T_2Y	$P_{T_2Y\|h}$	$P_{T_2Y\|s}$	$P_{T_2Y\|c}$
	T_2Z	$P_{T_2Z\|h}$	$P_{T_2Z\|s}$	$P_{T_2Z\|c}$

Table 3

The number of patients with each disease who provided information for each test in the probability matrix.

Table 3

		Disease I		
		1	2	3
	Test	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
J1	Age	93	51	51
J2	Clinical status	93	51	45
J3	Precipitin Test	91	43	30
J4	C.F. Test	43	39	37
J5	Serum globulins	47	27	27
J6	Gammaglobulin	37	19	15
J7	Thymol turbidity	47	42	31
J8	Zinc sulphate turbidity	27	10	17
J9	B.S.H.	40	45	32
J10	24 hour thyroidal ^{131}I uptake	89	48	40
J11	Duration	46	49	51
J12	Recent increase in size	52	50	47
J13	Estimated size of gland	93	51	49
J14	Nodular or diffuse	52	51	47
J15	Consistency	93	90	51

Table 3 (continued)

		Disease I		
		1	2	3
	Test	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
J16	Discomfort	53	49	44
J17	Tracheal deviation or compression on x-ray	52	45	40
J18	Laryngeal palsy	46	45	34
J19	Fixation to tissues	53	51	40
J20	Cervical lymph nodes	53	50	49
J21	P.B.^{127}I	30	37	13
J22	P.B.^{131}I	52	42	40
J23	Bb^{131}I	13	5	10
J24	$KClO_4$ Discharge	30	15	4
J25	Pyramidal lobe	53	51	46
J26	Pain in Goitre	53	46	44
J27	Hoarseness	52	49	49
J28	Dysphagia	52	48	46
J29	Choking or tightness	52	48	46
J30	Cough or stridor	51	45	47

Table 4

A typical computer print out.

Table 4

Only the results of clinical examination and history taking have been supplied as data to the machine in this case. Shown are the computer relative likelihoods of diagnosis for the patient together with the relative discriminating power of the tests remaining in the probability matrix.

PATIENT 26

IDENTIFICATION:

GIVEN:

FIXATION TO TISSUES	NO
CERVICAL LYMPH NODES	IMPALPABLE
PYRAMIDAL LOBE	ABSENT
PAIN IN GOITRE	NO
HOARSENESS	YES
DYSPHAGIA	NO
COUGH OR STRIDOR	YES
RECENT INCREASE IN SIZE	NO
NODULAR OR DIFFUSE	NODULAR
DURATION(YEARS)	10.1+
ESTIMATED SIZE OF GLAND(GRAMS)	201+
CONSISTENCY	SOFT
CLINICAL STATUS	EUTHYROID
AGE	31-60

THEN APPLYING THESE RESULTS TO THE COMPLETE SET OF DISEASES, THE 3 MOST LIKELY ARE, IN ORDER OF PREFERENCE :

	REL.LIKEL.(%)	FRAC.OPT.PAT.
NON-TOXIC GOITRE	100.000000	0.000033
HASHIMOTO'S DISEASE	8.865070	0.000004
THYROID CANCER	1.650511	0.000005

THE BEST SYMPTOMS AND TESTS FOR DISTINGUISHING BETWEEN THESE POSSIBILITIES ARE, IN ORDER OF PREFERENCE (TAKING THOSE WHOSE POWER IS GREATER THAN 0.50 OF THE MAXIMUM POWER SCORED):

	REL.DISCR.POWER
C.F.T.	1.0000
PRECIPITIN TEST	0.8377
PB127I	0.8337
THYMOL TURBIDITY	0.8179
BE131I	0.8094
TRACHEAL DEV. OR COMP. ON X-RAY	0.7868
E.S.R.	0.6923
GAMMAGLOBULIN	0.6891
PB131I AT 48 HOURS	0.6691
ZNSO4 TURBIDITY	0.5839
DISCOMFORT	0.5653
SERUM GLOBULINS	0.5370

Table 3

The calculated Bayesian probabilities of diagnosed and clinical diagnoses for 63 patients in whom the final diagnosis was Hashimoto's disease.

Table 5

* The final diagnosis was verified by histological examination of thyroid tissue

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goiter	Thyroid Cancer	
156*	Simple goitre	99.99	0.00	0.00	Calculated diagnosis correct by bo methods. Clinical diagnosis wrong.
157*	Thyroid cancer	0.12	97.64	2.23	Both methods and clinical diagnosis wrong. Calculated diagnosis diffe with method used.
158*	Thyroid cancer	99.97	0.00	0.02	Calculated diagnosis correct by bo methods. Clinical diagnosis wrong.
159*	Thyroid cancer Hashimoto's disease	96.83	0.00	3.16	Calculated diagnosis correct by bo methods. Clinical diagnosis wrong.
160*	Thyroid cancer Hashimoto's disease	99.99	0.00	0.00	Calculated diagnosis correct by bo methods. Clinical diagnosis wrong.

Table 5 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goiter	Thyroid Cancer	
161	Thyroid cancer Hashimoto's disease	99.96	0.03	0.00	Calculated diagnosis correct by bot methods. Clinical diagnosis wrong
162*	Thyroid cancer Hashimoto's disease	99.99	0.00	0.00	Calculated diagnosis correct by bot methods. Clinical diagnosis wrong
163*	Hashimoto's disease	99.97	0.00	0.02	
164	Hashimoto's disease	99.21	0.78	0.00	
165*	Thyroid cancer	99.9%	0.00	0.05	Calculated diagnosis correct by bot methods. Clinical diagnosis wrong.
166	Hashimoto's disease	25..2	74.56	0.20	
167	Hashimoto's disease	99.99	0.00	0.00	

Table 5 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
168	Hashimoto's disease	70.27	29.32	0.39	
169*	Thyroid cancer	99.98	0.00	0.01	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
170*	Thyroid cancer Hashimoto's disease	1.48	8.05	90.45	Calculated diagnosis wrong by both methods. Clinical diagnosis wrong.
171*	Simple goitre Hashimoto's disease	35.63	64.32	0.03	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability
172	Hashimoto's disease	95.97	0.00	0.02	

Table 5 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
173*	Thyroid cancer Hashimoto's disease	93.01	0.15	6.82	Calculated diagnosis not helpful enough using relative likelihood (and therefore wrong). Correct diagnosis using Bayesian probability Clinical diagnosis wrong.
174*	Thyroid cancer Hashimoto's disease	99.89	0.00	0.10	Calculated diagnosis correct by both methods. Clinical diagnosis wrong
175*	Thyroid cancer Hashimoto's disease	99.50	0.00	0.48	Calculated diagnosis correct by both methods. Clinical diagnosis wrong
176	Hashimoto's disease	33.31	66.64	0.04	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability Note final diagnosis made on clinical grounds.

Table 5 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goiter	Thyroid Cancer	
177*	Thyroid cancer	99.99	0.00	0.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
186	Hashimoto's disease	99.99	0.00	0.00	
201	Hashimoto's disease	99.99	0.00	0.00	
202	Hashimoto's disease	100.00	0.00	0.00	
203	Hashimoto's disease	99.99	0.00	0.00	
204*	Hashimoto's disease	99.99	0.00	0.00	
205*	Hashimoto's disease	99.99	0.00	0.00	
206*	Hashimoto's disease	99.94	0.00	0.05	
212	Hashimoto's disease	100.00	0.00	0.00	
219	Hashimoto's disease	99.99	0.00	0.00	

Table 5 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
220	Hashimoto's disease	93.79	0.00	6.29	Calculated diagnosis not helpful enough using relative likelihood (and therefore wrong). Correct diagnosis using Bayesian probability
221	Hashimoto's disease	99.99	0.00	0.00	
222	Hashimoto's disease	93.50	0.00	6.49	Calculated diagnosis not helpful enough using relative likelihood (and therefore wrong). Correct diagnosis using Bayesian probability. Clinical diagnosis correct.
223	Hashimoto's disease	99.99	0.00	0.00	
224	Hashimoto's disease	99.99	0.00	0.00	
225	Hashimoto's disease	100.00	0.00	0.00	
226	Hashimoto's disease	100.00	0.00	0.00	

Table 5 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
227*	Hashimoto's disease	99.97	0.03	0.02	
228	Hashimoto's disease	99.99	0.03	0.00	
229	Hashimoto's disease	99.99	0.03	0.00	
230	Hashimoto's disease	100.00	0.00	0.00	
231	Hashimoto's disease	100.00	0.00	0.00	

Table 6

The calculated Bayesian probabilities of diagnoses and clinical diagnoses for 27 patients in whom the final diagnosis was simple goitre.

Table 6

* The final diagnosis was verified by histological examination of thyroid tissue

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
180*	Thyroid cancer	74.20	25.78	0.02	Calculated diagnosis wrong using relative likelihood. Bayesian probability not helpful enough (and therefore wrong). Clinical diagnosis wrong.
181*	Simple goitre	1.16	72.27	26.55	Calculated diagnosis wrong by both methods. Clinical diagnosis corre
182	Simple goitre	99.98	0.00	0.01	
183	Simple goitre	99.99	0.00	0.00	
184*	Simple goitre	86.28	0.03	13.69	Calculated diagnosis wrong using relative likelihood. Correct diagnosis using Bayesian probabilit

Table 6 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
186	Simple goitre	99.57	0.00	0.42	
187	Simple goitre	92.69	0.04	7.25	
188	Simple goitre	99.99	0.00	0.00	
189	Simple goitre	99.94	0.00	0.05	
190*	Simple goitre	96.89	1.10	0.00	
191*	Simple goitre	41.23	0.52	58.24	Calculated diagnosis wrong by both methods. Clinical diagnosis correct
192*	Thyroid cancer Simple goitre	0.69	69.68	30.62	Both methods and clinical diagnosis wrong.
193	Simple goitre	99.37	0.01	0.62	
194*	Simple goitre	99.90	0.02	0.07	
195	Simple goitre	94.33	0.01	5.64	

Table 6 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
196*	Simple goitre	99.94	0.00	0.05	
197*	Simple goitre	99.99	0.00	0.00	
207	Simple goitre	99.99	0.00	0.00	
208	Simple goitre	99.99	0.00	0.00	
209	Simple goitre	99.96	0.03	0.00	
210	Simple goitre	99.92	0.00	0.06	
211	Simple goitre	99.84	0.09	0.05	
214	Simple goitre	99.97	0.01	0.01	
215	Simple goitre	99.88	0.00	0.02	

Table 6 (continued)

Case No.	Clinical Diagnosis	Bayesian Probability			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
216	Simple goitre	99.99	0.00	0.00	
217	Simple goitre	99.99	0.00	0.00	
218	Simple goitre	99.99	0.00	0.00	

Table 7

The calculated Bayesian probabilities of diagnoses and clinical diagnoses for 19 patients in whom the final diagnosis was thyroid cancer.

Table 7

* The final diagnosis was verified by histological examination of thyroid tissue

Case No.	Diagnosis	Bayesian Probability			Comment
		Thyroid Cancer	Hashimoto's Disease	Simple Goitre	
178*	Thyroid cancer	99.99	0.00	0.00	
179*	Thyroid cancer	99.99	0.00	0.00	
190*	Thyroid cancer	99.99	0.00	0.00	
199*	Thyroid cancer	99.99	0.00	0.00	
200*	Thyroid cancer	99.99	0.00	0.00	
213*	Thyroid cancer	100.00	0.00	0.00	
232*	Simple goitre Thyroid cancer	0.36	0.10	99.52	Calculated diagnosis wrong by both methods. Clinical diagnosis wrong.

Table 7 (continued)

Case No.	Diagnosis	Bayesian Probability			Comment
		Thyroid Cancer	Hashimoto's Disease	Simple Goitre	
233*	Thyroid cancer	99.99	0.00	0.00	
234*	Thyroid cancer	99.99	0.00	0.00	
235*	Thyroid cancer	1.13	2.07	96.79	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability. Clinical diagnosis correct.
236*	Thyroid cancer	99.99	0.00	0.00	
237*	Thyroid cancer	43.38	0.03	56.53	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability. Clinical diagnosis correct.

Table 7 (continued)

Case No.	Diagnosis	Bayesian Probability			Comment
		Thyroid Cancer	Hashimoto's Disease	Simple Goitre	
238*	Thyroid cancer	99.99	0.00	0.00	
239*	Thyroid cancer	94.77	0.76	4.45	
240*	Simple goitre	00.00	0.65	99.33	Both methods and clinical diagnosis wrong.
241*	Simple goitre	0.10	53.42	46.4	Both methods and clinical diagnosis wrong.
242*	Thyroid cancer	43.6	0.27	55.8	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability. Clinical diagnosis correct.
243*	Thyroid cancer	99.2	0.00	0.72	
244*	Thyroid cancer	99.95	0.00	0.04	

Table 6

The calculated relative likelihoods of diagnoses and clinical diagnoses for 43 patients in whom the final diagnosis was Hashimoto's disease.

Table 3

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
156*	Simple goitre	100.00	0.00	0.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
157*	Thyroid cancer	0.53	49.34	100.00	Both methods and clinical diagnosis wrong. Calculated diagnosis differs with method used.
158*	Thyroid cancer	100.00	0.00	0.29	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.

Table 8 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
159*	Thyroid cancer Hashimoto's disease	100.00	0.00	32.15	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
160*	Thyroid cancer Hashimoto's disease	100.00	0.00	0.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
161*	Thyroid cancer Hashimoto's disease	100.00	0.00	0.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
162*	Thyroid cancer Hashimoto's disease	100.00	0.00	0.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
163*	Hashimoto's disease	100.00	0.28	0.00	
164	Hashimoto's disease	100.00	0.09	0.00	

Table 6 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
165*	Thyroid cancer	100.00	0.00	0.54	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
166	Hashimoto's disease	100.00	33.31	4.71	
167	Hashimoto's disease	100.00	0.00	0.04	
168	Hashimoto's disease	100.00	4.13	5.38	
169*	Thyroid cancer	100.00	0.00	0.16	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
170*	Thyroid cancer Hashimoto's disease	0.16	0.10	100.00	Calculated diagnosis wrong by both methods. Clinical diagnosis wrong.

Table 3 (continued)

Case	Case No.	Clinical Diagnosis	Relative Likelihood			Comment
			Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
Cat	171*	Simple goitre Hashimoto's disease	100.00	23.15	0.97	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability. Clinical diagnosis wrong.
	172	Hashimoto's disease	100.00	0.00	0.21	
	173*	Thyroid cancer Hashimoto's disease	100.00	0.01	73.03	Calculated diagnosis not helpful using relative likelihood (and therefore wrong). Correct diagnosis using Bayesian probability. Clinical diagnosis wrong.
	174*	Thyroid cancer Hashimoto's disease	100.00	0.00	1.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.

Table 8 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
175*	Thyroid cancer Hashimoto's disease	100.00	0.00	4.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
176	Hashimoto's disease	100.00	22.30	1.91	Calculated diagnosis correct using selective likelihood. Wrong diagnosis using Bayesian probability. Note final diagnosis made on clinical grounds.
177*	Thyroid cancer	100.00	0.00	0.00	Calculated diagnosis correct by both methods. Clinical diagnosis wrong.
185	Hashimoto's disease	100.00	0.00	0.00	
201	Hashimoto's disease	100.00	0.00	0.00	
202	Hashimoto's disease	100.00	0.00	0.00	

Table 8 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
203	Hashimoto's disease	100.00	0.00	0.00	
204*	Hashimoto's disease	100.00	0.00	0.00	
205*	Hashimoto's disease	100.00	0.00	0.00	
206*	Hashimoto's disease	100.00	0.00	0.00	
212	Hashimoto's disease	100.00	0.00	0.00	
219	Hashimoto's disease	100.00	0.00	0.05	
220	Hashimoto's disease	100.00	0.00	67.00	Calculated diagnosis not helpful enough using relative likelihood (and therefore wrong). Correct diagnosis using Bayesian probability.

Table 2 (continued)

Case No.	Clinical Diagnosis	Selective Likelihood			Comment
		Hashimoto's Disease	Simple Goitre	Thyroid Cancer	
221	Hashimoto's disease	100.00	0.00	0.00	
222	Hashimoto's disease	100.00	0.00	0.00	Calculated diagnosis not helpful enough using selective likelihood (and therefore wrong). Correct diagnosis using Bayesian probability. Clinical diagnosis correct.
223	Hashimoto's disease	100.00	0.00	0.00	
224	Hashimoto's disease	100.00	0.00	0.00	
225	Hashimoto's disease	100.00	0.00	0.00	
226*	Hashimoto's disease	100.00	0.00	0.00	
227*	Hashimoto's disease	100.00	0.00	0.00	

Table 8 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comments
		Hashimoto's Disease	Simple Goiter	Thyroid Cancer	
228	Hashimoto's disease	100.00	0.00	0.00	
229	Hashimoto's disease	100.00	0.00	0.00	
230	Hashimoto's disease	100.00	0.00	0.00	
231	Hashimoto's disease	100.00	0.00	0.00	

Table 9

The calculated relative likelihoods of diagnoses and clinical diagnoses for 87 patients in whom the final diagnosis was simple goitre.

Table 9

* The final diagnosis was verified by histological examination of thyroid tissue

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
180*	Thyroid cancer	0.30	100.00	0.00	Calculated diagnosis wrong using relative likelihood. Bayesian probability not helpful enough (and therefore wrong). Clinical diagnosis wrong.
181*	Simple goitre	0.01	100.00	3.13	Calculated diagnosis wrong by both methods. Clinical diagnosis correct.
182	Simple goitre	100.00	0.00	0.12	
183	Simple goitre	100.00	0.00	0.00	

Table 9 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
185*	Simple goitre	75.34	2.12	100.00	Calculated diagnosis wrong using relative likelihood. Correct diagnosis using Bayesian probabilit
186	Simple goitre	100.00	3.12	0.10	
187	Simple goitre	100.00	4.01	69.10	
188	Simple goitre	100.00	0.00	0.00	
189	Simple goitre	100.00	0.03	0.61	
190*	Simple goitre	100.00	0.25	11.20	
191*	Simple goitre	8.65	0.16	100.00	Calculated diagnosis wrong by both methods. Clinical diagnosis corre

Table 9 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
192*	Thyroid cancer Simple goitre	0.00	100.00	4.01	Both methods and clinical diagnosis wrong.
193	Simple goitre	100.00	1.01	7.00	
194*	Simple goitre	100.00	1.00	0.66	
195	Simple goitre	100.00	1.51	53.13	
196*	Simple goitre	100.00	0.31	0.41	
197*	Simple goitre	100.00	0.00	0.01	
207	Simple goitre	100.00	0.15	0.00	
208	Simple goitre	100.00	0.02	0.03	

Table 9 (continued)

Case No.	Clinical Diagnosis	Relative Likelihood			Comment
		Simple Goitre	Thyroid Cancer	Hashimoto's Disease	
209	Simple goitre	100.00	3.15	0.01	
210	Simple goitre	100.00	7.23	0.69	
211	Simple goitre	100.00	8.03	0.42	
214	Simple goitre	100.00	1.05	0.16	
215	Simple goitre	100.00	7.13	0.25	
216	Simple goitre	100.00	0.78	0.01	
217	Simple goitre	100.00	0.85	0.03	
218	Simple goitre	100.00	0.18	0.00	

Table 10

The calculated relative likelihoods of diagnoses and clinical diagnoses for 19 patients in whom the final diagnosis was thyroid cancer.

Table 10 (continued)

Case No.	Diagnosis	Relative Likelihood			Comment
		Thyroid Cancer	Hashimoto's Disease	Simple Goitre	
238*	Thyroid cancer	100.00	0.00	0.00	
239*	Thyroid cancer	100.00	0.00	0.00	
240*	Simple goitre	0.69	5.81	100.00	Both methods and clinical diagnosis wrong.
241*	Simple goitre	2.35	100.00	9.14	Both methods and clinical diagnosis wrong.
242*	Thyroid cancer	100.00	0.06	1.73	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability Clinical diagnosis correct.
243*	Thyroid cancer	100.00	0.00	0.00	
244*	Thyroid cancer	100.00	0.00	0.00	

Table 20 (continued)

Case No.	Diagnosis	Relative Likelihood			Comment
		Thyroid Cancer	Hashimoto's Disease	Simple Goitre	
232*	Simple goitre Thyroid cancer	32.54	0.91	100.00	Calculated diagnosis wrong by both methods. Clinical diagnosis wrong.
233*	Thyroid cancer	100.00	0.00	0.00	
234*	Thyroid cancer	100.00	0.00	0.00	
235*	Thyroid cancer	100.00	10.91	99.31	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability Clinical diagnosis correct.
236*	Thyroid cancer	100.00	0.00	0.00	
237*	Thyroid cancer	100.00	0.02	1.59	Calculated diagnosis correct using relative likelihood. Wrong diagnosis using Bayesian probability Clinical diagnosis correct.

Table 10

* The final diagnosis was verified by histological examination of thyroid tissue

Case No.	Diagnosis	Relative Likelihood			Comment
		Thyroid Cancer	Hashimoto's Disease	Simple Goitre	
178*	Thyroid cancer	100.00	0.00	0.00	
179*	Thyroid cancer	100.00	0.00	0.00	
198*	Thyroid cancer	100.00	0.00	0.00	
199*	Thyroid cancer	100.00	0.00	0.00	
200*	Thyroid cancer	100.00	0.00	0.00	
213*	Thyroid cancer	100.00	0.00	0.00	

Table 11

A comparison of the clinical diagnoses and the diagnoses calculated using Bayesian probability for 89 patients with non-toxic goitre.

Table 11

Figures in brackets refer to percentages

* The criteria for the final diagnosis are described in the text

Final Diagnosis *	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
Number of patients	43	27	19
Clinical diagnosis correct Calculated diagnosis correct	26(60)	23(85)	13(68)
Clinical diagnosis correct Calculated diagnosis wrong	2(5)	2(8)	3(16)
Clinical diagnosis wrong Calculated diagnosis correct	12(28)	0(0)	0( )
Clinical diagnosis wrong Calculated diagnosis wrong	3(7)	2(8)	3(16)

Table 18

A comparison of the clinical diagnosis and the diagnosis calculated using relative likelihood for 89 patients with non-toxic goitre.

Table 12

Figures in brackets refer to percentages

* The criteria for the final diagnosis are described in the text

Final Diagnosis *	Hashimoto's Disease	Simple Goitre	Thyroid Cancer
Number of patients	43	27	19
Clinical diagnosis correct Calculated diagnosis correct	26(60)	21(81)	16(84)
Clinical diagnosis correct Calculated diagnosis wrong	2(5)	3(12)	0(0)
Clinical diagnosis wrong Calculated diagnosis correct	12(28)	0(0)	0(0)
Clinical diagnosis wrong Calculated diagnosis wrong	3(7)	2(8)	3(16)

Table 13

A comparison of the clinical diagnoses and the diagnoses calculated by the methods of relative likelihood and Bayesian probability in 43 patients with Hashimoto's disease.

Table 13

Numbers refer to patients' case numbers

Clinical Diagnosis Correct
Calculated Diagnosis Correct

Relative Likelihood	Bayesian Probability
163 164 166	163 164 167
167 168 178	168 172 185
176 185 201	201 202 203
202 203 204	204 205 206
205 206 212	212 219 220
219 221 223	221 222 223
224 225 226	224 225 226
227 228 229	227 228 229
230 231	230 231

Clinical Diagnosis Wrong
Calculated Diagnosis Correct

Relative Likelihood	Bayesian Probability
156 190 159	156 190 159
160 161 162	160 161 162
169 169 171	165 169 171
174 175 177	174 175 177

Clinical Diagnosis Correct
Calculated Diagnosis Wrong

Relative Likelihood	Bayesian Probability
220 222	166 176

Clinical Diagnosis Wrong
Calculated Diagnosis Wrong

Relative Likelihood	Bayesian Probability
157 170 173	157 170 171

Table 14

A comparison of the clinical diagnoses and the diagnoses calculated by the methods of relative likelihood and Bayesian probability in 27 patients with simple goitre.

Table 14

Numbers refer to patients' case numbers

Clinical Diagnosis Correct Calculated Diagnosis Correct		Clinical Diagnosis Wrong Calculated Diagnosis Correct	
Relative Likelihood	Bayesian Probability	Relative Likelihood	Bayesian Probability
182 183 186	182 183 184		
187 188 189	186 187 188		
190 193 194	189 190 193		
195 196 197	194 195 196		
207 208 209	197 207 208		
210 211 214	209 210 211		
215 216 217	214 215 216		
218	217 218		

Clinical Diagnosis Correct Calculated Diagnosis Wrong		Clinical Diagnosis Wrong Calculated Diagnosis Wrong	
Relative Likelihood	Bayesian Probability	Relative Likelihood	Bayesian Probability
181 184 191	181 191	180 192	180 192

Table 19

A comparison of the clinical diagnoses and the diagnoses calculated by the methods of relative likelihood and Bayesian probability in 19 patients with thyroid cancer.

Table 15

Numbers refer to patients' case numbers

Clinical Diagnosis Correct Calculated Diagnosis Correct		Clinical Diagnosis Wrong Calculated Diagnosis Correct	
Relative Likelihood	Bayesian Probability	Relative Likelihood	Bayesian Probability
178 179 190	178 179 190		
199 200 213	199 200 213		
233 234 235	233 234 236		
236 237 238	238 239 243		
239 242 243	244		
244			

Clinical Diagnosis Correct Calculated Diagnosis Wrong		Clinical Diagnosis Wrong Calculated Diagnosis Wrong	
Relative Likelihood	Bayesian Probability	Relative Likelihood	Bayesian Probability
	235 237 242	232 240 241	232 240 241

Table 16

Cases where the correct diagnosis was and was not considered in the differential diagnosis by the clinician and by calculation.

Table 16

Cases where the correct diagnosis was not considered in the differential diagnosis

		Case No.
Hashimoto's Disease	Clinical Diagnosis	156 157 158
	Relative Likelihood	157 170
	Bayesian Probability	157 170
Simple Goitre	Clinical Diagnosis	180
	Relative Likelihood	180 181 191 192
	Bayesian Probability	180 181 191 192
Thyroid Cancer	Clinical Diagnosis	240 241
	Relative Likelihood	240 241
	Bayesian Probability	232 235 240 241

Table 16 (continued)

Cases where the correct diagnosis was considered in the differential diagnosis

		Case No.
Hashimoto's Disease	Clinical Diagnosis	159 160 161 162 165 169 170 172 173 174 175 177
	Relative Likelihood	173 220 222
	Bayesian Probability	166 171 176
Simple Goitre	Clinical Diagnosis	192
	Relative Likelihood	194
	Bayesian Probability	189 191
Thyroid Cancer	Clinical Diagnosis	232
	Relative Likelihood	232
	Bayesian Probability	237 242

Table 17

A probability matrix demonstrating the fallaciously high likelihoods which may be computed when signs are interdependent.

Table 17

Test	Outcome	Hashimoto's Disease	Thyroid Cancer	Likelihood of cancer given by each test if Class I result is the outcome for that test
Thymol turbidity	I	0.25	0.97	$\frac{0.97}{0.25} = 3.9$
	II	0.28	0.30	
	III	0.47	0.00	
Thymol Flocculation	I	0.42	0.92	$\frac{0.92}{0.42} = 2.2$
	II	0.18	0.80	
	III	0.40	0.00	
Zinc sulphate turbidity	I	0.22	0.71	$\frac{0.71}{0.22} = 3.2$
	II	0.63	0.29	
	III	0.15	0.00	
Cephalin Cholesterol	I	0.39	0.83	$\frac{0.83}{0.39} = 2.1$
	II	0.28	0.17	
	III	0.33	0.00	
Colloidal Gold	I	0.35	0.42	$\frac{0.42}{0.35} = 1.2$
	II	0.16	0.33	
	III	0.49	0.25	

Likelihood of cancer if Class I result is the outcome for all tests $= \frac{0.97 \times 0.92 \times 0.71 \times 0.83 \times 0.42}{0.25 \times 0.42 \times 0.22 \times 0.39 \times 0.35} = 69.2$

PART 3

APPENDICES

Appendix A

Details of the 195 patients who provided data for the probability matrix shown in Table 1 (p347). Myxoma was confirmed by histological examination of thyroid tissue in all cases.

Appendix A

J_1 to J_{30} refer to the tests performed on these patients.

The units in which the results of these tests were expressed and the key to the tests themselves are shown in Table 1.

H = Hashimoto's disease S = Simple goitre C = Thyroid cancer

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
1	H	78	Eu	-	-						
2	"	56	Hypo	+	++	2.4	1.42	8		16	
3	"	52	Eu	+	+	2.3	1.34	4		16	
4	"	63	Hypo	+	++	3.0	1.66	12	40	7	

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
5	"	63	Ba	-	++	2.1	0.79	6	35	37	
6	"	62	Ba	+	++	2.2	1.03	4	17	4	
7	"	49	Hypo	+	++	4.3	0.54	6		66	
8	"	63	Ba	+	-	3.2	1.51	1	24	34	
9	"	52	Hypo	+	++	2.3	1.40	14		48	
10	"	37	? ?	-	++	2.0	0.59	5		5	
11	"	45	? ?	+	++	2.1	0.98	3	22	15	
12	"	67	Ba	+	++						
13	"	27	Ba	+	++	3.0	1.74	10		14	
14	"	57	Hypo	+	++	2.3	1.16	8		30	

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
15	N	49	Bu	-	++	2.2	1.09	5	27	30	
16	"	45	Hypo	+	+	2.0	1.22	12		32	
17	"	52	Bu	-	++	2.4	1.20	3	10	22	
18	"	65	Hypo	+	++	3.5	0.66	3	9	6	
19	"	48	Bu	-	-	2.9	2.05	7		12	
20	"	63	? B	+	++	2.3	1.18	4	25	20	
21	"	56	Bu	+	++	3.5	0.77	19	68	57	
22	"	44	Hypo	+	++	1.8	0.71	1		8	
23	"	53	Hypo	+	++	2.8	0.74	1	3	46	
24	"	49	Bu	+	++	2.6	1.63	2	25	7	27

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
25	II	46	E	+	++	2.2	1.13	15		26	61
26	"	55	Hypo	-	++	1.8	0.78	1	18	13	45
27	"	46	Hypo	+	++	2.5	1.19	4		16	33
28	"	55	Eu	+	++	2.1	1.28	5	16	27	41
29	"	53	Eu	+	++	4.0	2.53	10	33	51	26
30	"	44	Hypo	-	++	1.9	0.60	1	13	15	38
31	"	51	Eu	+	++	2.7	1.51	2	21	9	39
32	"	47	Eu	+	++	3.3	1.48	8	22	28	47
33	"	70	Eu	+	++	4.1	1.53	9	23	39	35
34	"	44	Eu	+	++	2.8	1.11	3	17	19	68

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
35	E	48	Ba	-	++						39
36	"	43	Ba	-	++	2.0	0.84	1	10	83	55
37	"	38	Hypo	+	++	2.0	0.75	2	3	38	50
38	"	32	Ba	+	++						46
39	"	71	Ba	-	++	2.9	1.41	2	11	13	65
40	"	47	Ba	-	++	2.7	1.56	4	10	7	58
41	"	39	Hypo	+	++	1.9		3	14	26	31
42	"	71	Hypo	-	+	1.9	0.71	1		15	
43	"	53	Hypo	+		3.8		6		22	67
44	"	12	Ba	+		3.1		6	9	5	65

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
45	"	49	Eu	+		3.1		2		7	27
46	"	47	Eu	+						25	46
47	"	52	Eu	-		4.6		12		69	43
48	"	57	Ergo	-		3.4		8		23	39
49	"	62	Eu	+		5.9		37		73	50
50	"	52	Eu								35
51	"	46	Eu	+		3.1		8		25	58
52	"	57	Eu			3.3		6		24	42
53	"	66	Eu	+		4.9		9		77	32
54	S	43	Eu	-	-	1.6		2	3	5	39

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
55	S	29	Ba	-	-	1.9	0.71	2		8	35
56	"	33	Ba	-	-	1.7	0.73	1	10	7	48
57	"	49	Ba	-	-	2.0	0.75	2		2	26
58	"	21	Ba	-	-	2.1		1	11	11	71
59	"	45	Ba	-	-	1.8	0.81	2	20	11	
60	"	44	Ba	-	+	2.0	0.61	3		9	45
61	"	20	Ba	-	-	2.1	0.73	4	8		57
62	"	50	Ba	-	-	1.7	0.75	2	12	3	30
63	"	25	Ba	-	-	2.4	0.81	1	19	6	28
64	"	43	Ba	-	-			1		3	51

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
65	S	32	Eu	-	-	2.1	0.80	2		16	56
66	"	31	Eu	-	-			2	10	4	32
67	"	45	Eu	-	-	1.9	0.51	2		2	59
68	"	25	Eu	-	-	2.1	1.30	1	6	9	33
69	"	26	Eu	-	-			2		7	53
70	"	53	Eu	-	-			3	9	11	60
71	"	16	Eu	-	-	1.8	0.65	1	8	5	29
72	"	18	Eu	-	-			1		8	41
73	"	43	Eu	-	-	1.5	0.81	1	17	6	65
74	"	41	Eu	-	-	1.9	0.72	2		5	52

Appendix A (continued)

Case No.	Blocks	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
75	8	20	Ba	-	-			1	16	1	58
76	"	43	Ba	-	-	1.2		1		3	45
77	"	24	Ba	-	-	1.9	0.69	2		5	43
78	"	41	Ba	-	-			3	15	2	52
79	"	56	Ba	-	-	1.7	0.82	2	3	3	57
80	"	40	Ba	-	-	1.9	0.83	1		10	36
81	"	31	Ba	-	-	2.0		1		2	69
82	"	65	Ba	-	-			2		6	59
83	"	31	Ba	-	-	1.9		2		7	49
84	"	56	Ba	-	-		0.75		11	8	58

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
85	S	49	Ea	-	+	2.2		1		3	78
86	"	38	Ea	-	-			4		4	59
87	"	52	Ea	-	-			1		8	70
88	"	22	Ea	-	-			2	19	12	48
89	"	31	Ea	-	-			2	17	11	31
90	"	37	Ea	-	-			1		5	47
91	"	23	Ea	-	-			2		9	
92	"	35	Ea	-	-			2		3	55
93	"	43	Ea							6	45
94	"	59	Ea							10	39

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
95	S	38	Eu			2.6		2		4	61
96	"	40	Eu	-		2.7		1		12	54
97	"	18	Eu							0	26
98	"	45	Eu							3	61
99	"	65	Eu	-		3.2		1		5	48
100	"	29	Eu								52
101	"	47	Eu	-						5	45
102	"	65	Eu								60
103	"	71	Eu			3.0		1			47
104	"	31	Eu	-							51

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
105	C	77	Ex	-	-			2			45
106	"	56	Ex	-	-						31
107	"	73	Ex	-	+					10	36
108	"	57	Ex	-	-	2.1	0.71		16		24
109	"	72	Ex	-	-	1.8	0.89			19	52
110	"	71	Ex	+	+						43
111	"	61	Ex	-	-					8	29
112	"	65	Ex	-	-			1	9	24	39
113	"	54	Ex	-	-					95	36
114	"	50	Ex	+	-						24

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
115	0	17	Ex	-	-	2.1	0.91	2	13	36	35
116	"	75	Ex	-	-	2.1	0.69	2	9		17
117	"	60	Ex	+	+	1.9	0.80	1	9	25	26
118	"	36	Ex	-	-	1.9	0.71	2	6	18	59
119	"	30	Ex	-	-	1.7	0.85	1	5	7	50
120	"	72	Ex	-	-	1.6	0.81	1	19		35
121	"	48	Ex	-	-	1.8	0.60	2	8	5	25
122	"	20	Ex	-	-	2.6	0.75	1	7		48
123	"	66	Ex	-	-	1.8	0.89	2	8	5	46
124	"	64	Ex	-	-	2.0	0.69	1	23	18	23

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
125	S	71	Bu	-	-	1.8	0.67	2		65	50
126	"	73	Bu	-	-	1.9	0.90	4			39
127	"	61	Bu	-	+	2.1		1			31
128	"	69	Bu	-	-	2.0	0.05	1		68	58
129	"	74	Bu	-	-	2.1		2			27
130	"	69	Bu	-	-			2			45
131	"	45	Bu	-	-						33
132	"	36	Bu	-	-						35
133	"	39		-	-			2	12	6	61
134	"	24		-	-			2	13	8	28

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
135	"	63		-	-			1	9	42	65
136	"	61		-	-			2	15		23
137	"	39		-	-			2	7		
138	"	64		-	-	3.5		2		6	19
139	"	70	Ex		-	3.2		2		76	27
140	"	55	Ex	-	-					15	43
141	"	31	Ex		-					11	56
142	"	50	Ex	-						89	21
143	"	41	Ex							4	42
144	"	65	Ex			3.1		1		84	20

Appendix A (continued)

Case No.	Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
145	C	59	Eu	-		3.7		2		5	35
146	"	41	Eu							33	
147	"	73	Eu			3.0		1		108	19
148	"	76	Eu			3.4		1		23	42
149	"	67	Eu	-		2.0		1		5	
150	"	82	Eu							10	43
151	"	46	Eu							2	53
152	"	65	? T	+		5.0				73	71[@]
153	"	82	Eu			4.1		1		63	45
154	"	74	Eu							15	44
155	"	53	Eu			2.7				16	33

Operation à (continued)

Case No.	Regions	s_{11}	s_{12}	s_{13}	s_{14}	s_{15}	s_{16}	s_{17}	s_{18}	s_{19}	s_{20}
1		647		250		2000					
2		1040		75		2000					
3		840		100		2000					
4		450		150		2000					
5		549		300		2000					
6		653		50		2000					
7		641		50		2000					
8		945		200		2000					
9		450		200		2000					
10		549		200		2000					

Appendix A (continued)

Core No.	Magnesia	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
11	"	0.3	-	75	-	Rare	+	-	-	-	-
12	"	0.9	+	350	-	Rare	+	+	-	-	-
13	"		-	75	-	Rare	-	+	-	-	-
14	"	0.3	-	75	+	Rare	-	-	-	-	-
15	"		-	75	-	Rare	-	-	-	-	-
16	"	3.0	-	100	-	Rare	-	-	-	-	-
17	"	5.0	-	75	+	Rare	-	-	-	-	-
18	"	1.0	+	75	+	Rare	-	-	-	-	-
19	"	0.7	-	75	-	Rare	+	-	-	-	-
20	"	3.0	-	300	+	Rare	-	+	-	-	-

Appendix 1 (continued)

Case No.	Diagnosis	x_{11}	x_{12}	x_{13}	x_{14}	x_{15}	x_{16}	x_{17}	x_{18}	x_{19}	x_{20}
21	"	1.0	-	150	+	Rash	-	+	-	-	-
22	"	3.0	-	200	-	Flem	-	-	-	-	-
23	"		-	100	+	Flem	-	-	-	-	-
24	"	10.0	-	150	-	Flem	-	-	-	-	-
25	"	15.0	-	225	-	Soft	-	-	-	-	-
26	"		-	75	-	Flem	-	-	-	-	-
27	"	6.0	-	200	+	Flem	-	+	-	-	+
28	"	7.0	-	175	-	Flem	-	-	-	-	-
29	"	4.0	+	285	+	Rash	-	-	-	-	-
30	"	1.0	-	100	+	Flem	-	-	-	-	-

Appendix A (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
41	E		-	50	+	Rim	-	-	-	-	-
42	"	5.0	-	75	-	Rim	-	-	-	-	-
43	"	0.4	+	35	+	Rim	-	-		-	-
44	"	3.0	+	300		Rim	-	-		-	-
45	"	3.0	+	50	-	Rim	-			-	-
46	"	5.0	+	250	+	Rim	-	+	-	-	-
47	"	5.0	+	125	+	Rim	-	+		-	-
48	"	6.0	+	150	+	Rim	-	+	-	-	-
49	"			200	+	Rim	-	+	-	-	-
50	"	0.5	-	50	+	Rim	-	-	-	-	-

Appendix A (continued)

Case No.	Diagnosis	j_{11}	j_{12}	j_{13}	j_{14}	j_{15}	j_{16}	j_{17}	j_{18}	j_{19}	j_{20}
31	"	4.0	-	75	-	Fixn	-	-	-	-	-
32	"	1.0	-	350	-	Fixn	-	-	-	-	-
33	"	3.0	+	200	+	Fixn	-	-	-	-	-
34	"	6.0	-	50	-	Fixn	-	-	-	-	-
35	"	29.0	-	150	-	Sesh	-	+	-	-	-
36	"	3.0	-	50	+	Fixn	-	-	-	-	-
37	"		-	75	+	Fixn	-	-	-	-	-
38	"	2.0	+	50	-	Fixn	-	-	-	-	-
39	"	3.0	+	200	+	Fixn	-	-	-	-	-
40	"	1.0	-	50	-	Fixn	-	-	-	-	-

Appendix A (continued)

Core No.	Magnetic	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
51	E	0.3	+	250	+	Rim	-	-		-	-
52	"	0.6	+	150	+	Rim	-	-		-	-
53	"	1.0	+	150	+	Rim	-	-		-	-
54	S	19.0	-	75	-	Soft	-	-	-	-	-
55	"	9.0	-	75	-	Soft	-	-	-	-	-
56	"	3.0	-	50	+	Soft	-	-	-	-	-
57	"	16.0	-	50	-	Rim	+	-	-	-	-
58	"	16.0	-	75	-	Soft	-	-	-	-	-
59	"	9.0	-	100	-	Rim	+	-	-	-	-
60	"	1.0	-	100	+	Rim	-	-	-	+	-

Appendix I (continued)

Case No.	Diagnosis	d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}	d_{19}	d_{20}
61	S	11.0	-	75	-	Soft	+	-	-	+	-
62	"	1.0	-	75	-	Firm	-	-	+	-	-
63	"	9.0	-	75	-	Firm	+	-	-	-	-
64	"	4.0	-	100	-	Soft	-	-	-	-	-
65	"	28.0	-	300	-	Soft	+	-	-	-	-
66	"	32.0	+	300	+	Soft	-	-	-	-	-
67	"	0.7	-	75	-	Firm	+	-	-	-	-
68	"	4.0	+	250	-	Soft	-	-	-	-	-
69	"	8.0	-	50	+	Soft	-	-	-	-	-
70	"	25.0	-	100	-	Firm	+	-	-	-	-

Appendix A (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
72	S	6.0	-	120	+	Firm	+	+	+	+	+
72	"	11.0		100	+	Soft	+	+	+	+	+
73	"	29.0	+	300	-	Soft	+	+	+	+	+
74	"	3.0	+	50	+	Firm	+	+	+	+	-
75	"	37.0	-	50	-	Firm	+	+	+	+	-
76	"	25.0	+	75	+	Soft	+	+	+	+	+
77	"	0.1	-	100	+	Soft	+	-	+	+	-
78	"	2.0	+	50	+	Soft	+	+	+	+	-
79	"	10.0	-	75	+	Firm	+	+	+	+	+
80	"	3.0	-	100	+	Firm	+	+	+	+	+

Appendix A (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
61	S	9.0	-	75	-	Rem	+	-	-	+	-
62	"		-	75	+	Rem	-	-	+	-	+
63	"	8.0	-	50	-	Sc24	+	-	-	+	+
64	"	2.0	-	75	+	Rem	+	+	-	+	+
65	"		-	250	-	Sc23	+	-	-	-	-
66	"	6.0	-	100	-	Rem	+	-	-	-	+
67	"	3.0	+	100	+	Sc25	-	-	-	+	+
68	"	3.0	-	75	+	Sc29	-	-	-	-	+
69	"	4.0	-	50	-	Rem	-	+	-	+	+
70	"	7.0	+	75	+	Rem	+	-	+	-	+

Appendix A (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
91	S	5.0	+	75	+	Plm	+	-	-	+	-
92	"	2.0	-	50	+	Plm	+	-	-	-	-
93	"	12.0	+	50	-	Plm	+		-	-	-
94	"	15.0	-	100	+	Plm	-	+		-	+
95	"	5.0	-	75	+	Plm	-			-	-
96	"	24.0	-	450	+		-	+		+	-
97	"	0.9	-	50	+	Plm	+	+	-	-	+
98	"	30.0	-	250	+	Mod	-	-		-	
99	"		-	125	+	Plm	-	+		-	-
100	"	0.3	+	75	+	Plm				-	-

Appendix 1 (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
101	S	16.0	-	75	-	Plan	-			-	-
102	"	0.4	+	100	-	Plan				-	-
103	"	30.0	-	100	+	Bast		+	-	+	-
104	"	6.1	+	50	+	Plan	-			-	-
105	"	9.0	+	100	+	Plan	-	+	-	-	-
106	"	1.0	+	100	+	Bast	+	+	-	+	-
107	"	1.0	+	75	+	Bast	-	+	+	+	-
108	"	0.5	+	75	+	Bast	+	+	-	+	-
109	"	8.0	+	150	+	Bast	+		+	+	+
110	"	0.9	+	100	+	Bast	+	+	-	+	+

Appendix A (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
111	c	5.0	+	75	+	Rim	-	+	-	-	-
112	c	0.7	+	150		Rim	+	+	-	+	-
113	c	0.3	+	75	+	Rim	-	-	-	-	-
114	c	0.2	+	150		Rim	+	+	-	-	-
115	c	4.0	-	75	-	Rim	-	+	-	+	+
116	c	9.0	+	150	+	Rim	+	+	-	+	-
117	c	12.0	+	150	+	Rim	+	+	+	+	+
118	c	3.0	+	100	+	Rim	-	+	-	-	+
119	c	3.0	+	75	+	Rim	-	-	-	+	-
120	c	1.0	+	100	+	Rim	+	+	-	-	+

Appendix A (continued)

Case No.	Diagnosis	f_{11}	f_{12}	f_{13}	f_{14}	f_{15}	f_{16}	f_{17}	f_{18}	f_{19}	f_{20}
121	"	7.0	+	150	+	Plan	-	+	-	+	-
122	"	6.0	+	100	+	Plan	+	-	-	+	+
123	"	30.0	+	300	+	Band	-	+	-	-	-
124	"	1.0	+	150	+	Plan	+	+	-	+	-
125	"	2.0	-	160	-	Plan	.	+	-	+	-
126	"	0.7	-	150	+	Band	.	+	-	-	-
127	"	0.3	+	100	+	Plan	+	+	+	+	+
128	"	0.3	+	150	-	Band	+	+	-	-	-
129	"	3.0	+	75	+	Band	+	+	-	+	+
130	"	2.0	+	100	+	Band	+	+	+	+	-

Appendix 1 (continued)

Case No.	Diagnosis	d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}	d_{19}	d_{20}
131	"	0.4	+	180	+	Rect	+	+	-	+	-
132	"	0.2	+	150	+	Rect	-	+	-	-	-
133	"	2.0		190	+	Fem					
134	"	1.0		185	+	Fem					
135	"	2.0	+	125	-	Rect		+		+	-
136	"	0.5		180	-	Rect		+	+	+	+
137	"	4.0		190	+	Fem		-		-	+
138	"	0.2	+	75	+	Rect	-	-		+	-
139	"	0.6	-		-	Rect	-	+		-	+
140	"	0.2	+	100	-	Rect	+	+	-	+	+

Appendix A (continued)

Case No.	Diagnosis	d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}	d_{19}	d_{20}
141	"	15.0	+	50	+	Fem	-	+		-	+
142	"	4.0	+			Fem	-	+		-	-
143	"	2.0	+	50	+	Mal	+	-		-	+
144	"	4.0	+	50	-	Fem	-	+		-	+
145	"	3.0	+	150	+	Mal	+	+		+	+
146	"	4.0	+	50	+	Fem	-	-		-	-
147	"	2.0	+	150	+	Mal	+	+	+	+	+
148	"	0.4	+	50	-	Mal	-	-	-		+
149	"	3.0	+	50	+	Fem	-	-	-	+	+
150	"	20.0	+	100	+	Mal	+	+		+	-

Appendix A (continued)

Case No.	Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
151	"	20	-	50	+	Flex	+	-		-	+
152	"	40	+	150	+	Ext	-	+		+	-
153	"	6.1	+	150		Ext	+	+		-	+
154	"	30.0	+	250	+	Ext	-	+		+	+
155	"	5.2	+		-	Ext	+	+	+	+	-

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
1	"	3.2	0.39	77		+	+	+	+	+	+
2	"	0.6	0.26		+	+	+	+	+	+	+
3	"	2.6	0.64		+	+	+	+	+	+	+
4	"	0.7	0.48		+	+	+	+	+	+	+
5	"	3.1	0.22		+	+	+	+	+	+	+
6	"	2.5	0.05	82	+	+	+	+	+	+	+
7	"	1.6	0.36		+	+	+	+	+	+	+
8	"	3.1	0.23		+	+	+	+	+	+	+
9	"	1.1	0.36		+	+	+	+	+	+	+
10	"	3.6	0.49		+	+	+	+	+	+	+

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
11	"	5.3	0.42		+	+	-	-	-	+	-
12	"	3.1	2.74		-	-	-	-	+	+	-
13	"	4.8	0.85		-	-	-	+	-	-	-
14	"	0.7	0.18		+	-	-	-	-	-	-
15	"	2.8	0.32		-	-	-	+	-	+	-
16	"	0.8	0.13			-	-	-	-	-	-
17	"	0.3	1.38		-	-	-	-	-	+	-
18	"	3.7	0.18			-	-	-	-	-	-
19	"	2.5	0.05			-	-	-	-	-	-
20	"	4.6	0.46		+	-	-	-	-	-	-

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
21	"	3.1	0.39		+	-	+	+	+	+	+
22	"	2.1	0.23			+	+	+	+	+	+
23	"		0.95			+	+	+	+	+	+
24	"	4.4	0.36	39	+	+	+	+	+	+	+
25	"	2.9	0.29		+	+	+	+	+	+	+
26	"	2.1	0.31			+	+	+	+	+	+
27	"	1.9	0.25			+	+	+	+	+	+
28	"	1.5	0.28		+	+	+	+	+	+	+
29	"	2.5	0.96	33	+	+	+	+	+	+	+
30	"	2.1	0.28		+	+	+	+	+	+	+

Appendix A (continued)

Case No.	Diagnosis	J_{22}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
31	"	2.8	0.15		+	-	-	-	-	-	-
32	"	3.9	0.45	50		-	-	-	-	-	-
33	"	2.9	0.23			-	-	-	-	+	-
34	"	2.3	0.21			-	-	-	+	+	-
35	"	1.2	0.11		-	-	-	-	-	-	-
36	"	2.6	0.71	39		-	-	-	-	-	-
37	"	2.0	0.05			-	-	-	-	-	-
38	"		0.61	40		-	-	-	-	-	-
39	"		1.12			-	-	-	-	-	-
40	"	2.0	1.31	63		-	-	-	-	-	-

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
41	"		0.35			-	-	-	-	-	-
42	"					-	-	-	-	-	-
43	"		0.47	56		+	-	-	-	+	-
44	"	4.9	0.26	68		-	-				
45	"		0.37	60		-	-	-	+	-	-
46	"		0.27			-	-	-	+	-	-
47	"		0.26	51	+	-	-	-	+	+	-
48	"		0.80			-	-	-	-	-	-
49	"		0.22		-	-	-	-	+	-	-
50	"		0.80		-	-	-	-	-	-	-

Appendix A (continued)

Case No.	Diagonals	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
51	3		1.46	99	"	"	"	"	"	"	"
52	"		0.25		"	"	"	"	"	"	"
53	"		0.60		"	"	"	"	"	"	"
54	5	3.9				"	"	"	"	"	"
55	"	4.2			"	"		"	"	"	"
56	"	6.5				"		"	"	"	"
57	"	5.1			"	"	"	"	"	"	"
58	"	5.2				"	"	"	"	"	
59	"	3.9				"	"	"	"	"	"
60	"	4.8			"	"	"	"	"	"	"

Appendix A (continued)

Case No.	Vegetable	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
61	"	3.8				"	"	"	"	"	"
62	"	7.8			"	"	"	"	"	"	"
63	"					"	"	"	"	"	
64	"					"	"	"	"	"	"
65	"	6.1				"	"	"	"	"	"
66	"	3.9			"	"	"	"	"	"	"
67	"	6.4			"	"	"	"	"	"	"
68	"	5.3	0.00		"	"	"	"	"	"	"
69	"	5.9	0.00		"	"	"	"	"	"	"
70	"	5.2	0.00		"	"	"	"	"	"	"

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
71	"	6.9	0.29		"	"	"	"	"	"	"
72	"	5.8	0.00		"	"	"	"	"	"	"
73	"	7.0	0.22		"	"	"	"	"	"	"
74	"	5.9	0.00		"	"	"	"	"	"	"
75	"	3.5	0.00		"	"	"	"	"	"	"
76	"	3.7	0.24		"	"	"	"	"	"	"
77	"	4.9	0.00			"	"	"	"	"	"
78	"	4.9	0.00			"	"	"	"	"	"
79	"	3.8	0.00			"	"	"	"	"	"
80	"	4.5	0.41	73		"	"	"	"	"	"

Appendix A (continued)

Case No.	Response	δ_{22}	δ_{22}	δ_{23}	δ_{24}	δ_{25}	δ_{26}	δ_{27}	δ_{28}	δ_{29}	δ_{30}
81	S	5.1	0.23	95							
82	"	2.9	0.25								
83	"	4.9	0.13								
84	"	5.9	0.00								
85	"	5.3	0.03								
86	"	5.4	0.03								
87	"	5.2	0.08								
88	"	3.9	0.03								
89	"	5.9	0.09								
90	"	4.8	0.12								

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
91	S	4.8	0.05			-		+	-		
92	"	4.4	0.10			-		+	-	+	
93	"		0.00			+	-	-			-
94	"		0.00			+	-	+			-
95	"		0.25	93		-	-	+		+	-
96	"		0.00			-	+		+	-	+
97	"		0.00			-	-	+	+	+	-
98	"		0.00			-	+		+	+	-
99	"		0.00			-	-	-	+	+	+
100	"		0.10			+	+	+	-	-	+

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
101	S		0.25	99		-	-		+	+	-
102	"		0.60			-	-	+	+	-	-
103	"		0.13			-	+	-	-	-	+
104	"		0.93	83		-	-	-	-	-	-
105	"		0.17			-		+	-	-	-
106	"					-	-	+	-	+	-
107	"	3.1	0.10			-	-	+	+	-	+
108	"						-	+	-	+	-
109	"		0.53	85		-	+	-	-		-
110	"					-	-	+	-	-	+

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
111	"	7.8	1.10	93		-	-	-	+	-	-
112	"	9.3	0.39			-	+	+	+	-	-
113	"	3.0	0.09			-	-	-	-	+	-
114	"	4.6	0.08			-	-	+			
115	"	5.9				-	-	+	-	+	-
116	"	3.2	0.10			-	-	+	+	+	+
117	"	3.9	0.15			-	+	+	+	-	+
118	"	4.9	0.00			-	-	-	-	+	-
119	"	4.5	0.09			-	-	-	-	-	-
120	"	4.8				-	+	-	-	+	-

Appendix A (continued)

Case No.	Diagonals	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
121	5	4.9	0.05			-	-	-	-	+	-
122	5	4.3	0.00			-	-	-	-	-	-
123	5		0.08			-	-	-	-	+	-
124	5		0.33			-	+	-	-	+	-
125	5					-		-	-	+	-
126	5		0.31			-		+	-	-	-
127	5		0.05			-	+	+	+	+	+
128	5		0.14			-	+	-	-	-	-
129	5		0.29			-	+	+	+	+	-
130	5					-	+	+	-	+	+

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
131	+					+	+	+	+	+	+
132	+						+	+	+	+	+
133	+		0.05		+	+	+		+		
134	+		0.34		+	+	+		+		
135	+		0.23			+			+		+
136	+		0.39		+		+	+	+	+	+
137	+		0.05		+	+		+	+	+	
138	+		0.14	100		+		+		+	+
139	+		0.03			+		+	+	+	+
140	+		0.72	92		+	+	+	+	+	+

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
142	S		0.70	20		-	-	-		-	-
142	"		0.00			-	-	-	-	+	-
143	"		0.00			-	-	-	-	-	-
144	"		0.00			-	+	-		-	-
145	"		0.29	50		+	-	+	-	+	-
146	"					-	-	-	-	-	-
147	"		0.41	57			+	+	+	+	+
148	"		0.23			+	+	+	-	+	-
149	"					-	-	-	-	-	-
150	"		0.00			-	-	-	+	-	-

Appendix A (continued)

Case No.	Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
151	"	0.06				-	-	-	-	-	-
152	"	1.40	83			-	-	-		+	-
153	"	0.18	100			-	+	-	-	+	-
154	"	0.22	90				-	-	-	-	+
155	"	0.08				-	-	-	+	-	+

Appendix B

Details of the 89 patients who were submitted to computer calculated diagnosis in the assessment of the effectiveness of the probability matrix as an aid to diagnosis.

Appendix 3

The key to tests J_1 to J_{10} is shown in Table 1 ( ). This table also shows the units in which the outcome of each test was expressed.

\+ H = Hashimoto's disease S = Simple goitre C = Thyroid cancer

++ Eu = Euthyroid Hypo = Hypothyroid

* Diagnosis verified by histological examination of thyroid tissue in this patient.

Case No.	Final Diagnosis +	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
156	S*	31-60	Eu++	-		>2.2		>5			>60
157	S*	31-60	Eu	+		0-2.2		0-2			0-30
158	S*	31-60	Eu	-		>2.2		3-5		>40	>60
159	S*	>60	Hypo					>5		>40	0-30

Appendix 3 (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
160	Hyp	31-60	Hn	-		> 2.2		> 5			> 60
161	"	31-60	Hn	-		> 2.2		> 5			31-60
162	"	31-60	Hn	+	+	> 2.2		3-5		> 40	31-60
163	"	31-60	Hypo	-		> 2.2		> 5		> 40	31-60
164	"	31-60	Hypo	-		> 2.2		3-5			0-30
165	"	31-60	Hn	+		> 2.2	> 0.9	> 5			31-60
166	"	> 60	Hn			> 2.2		0-2			0-30
167	"	31-60	Hypo	-	-	> 2.2		> 5		21-40	31-60
168	"	31-60	Hn	-		> 2.2		0-2			31-60
169	"	31-60	Hypo	+	-						31-60

Appendix B (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
170	E*	>60	En	-		>2.2		0-2			31-60
171	E*	31-60	En	-		>2.2		1-5			31-60
172	E	31-60	En	+		>2.2		>5			31-60
173	E*	>60	En	-		>2.2		>5		0-20	31-60
174	E*	31-60	Hypo			>2.2		>5		21-40	0-30
175	E*	31-60	En	-		>2.2		>5		21-40	31-60
176	E*	31-60	En							0-20	31-60
177	E*	0-30	En	+		>2.2		>5		0-20	31-60
178	E*	>60	En	-		>2.2		0-2		0-20	0-30
179	E*	31-60	En	-		>2.2		0-2		>40	

Appendix B (continue)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
180	S*	>60	Ba	-		>2.2		0-2		0-20	31-60
181	S*	31-60	Ba			>2.2		0-2		21-40	31-60
182	S	0-30	Ba								31-60
183	S	31-60	Ba								
184	S*	31-60	Ba								31-60
185	H	0-30	Ba	+	++	>2.2		0-2			>60
186	S	31-60	Ba								>60
187	S	0-30	Ba								0-30
188	S	31-60	Ba								
189	S	31-60	Ba			>2.2		0-2		0-20	>60

Appendix B (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
190	[illegible]	31-60	Eu							0-20	> 60
191	[illegible]	31-60	Eu			2.2		3-5		0-20	31-60
192	[illegible]	31-60	Eu							21-40	31-60
193	[illegible]	0-30	Eu							0-20	31-60
194	[illegible]	31-60	Eu	-		0-2.2		0-2		0-20	31-60
195	[illegible]	31-60	Eu								31-60
196	[illegible]	31-60	Eu	-						0-20	> 60
197	[illegible]	0-30	Eu	-						0-20	> 60
198	[illegible]		Eu			> 2.2				21-40	31-60
199	[illegible]	> 60	Eu								31-60

Appendix B (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
200	[illegible]	>60	Eu			0-2.2		0-2		>40	31-60
201	[illegible]	>60	Hypo	-	+	>2.2	>0.9	3-5	13-25	21-40	31-60
202	[illegible]	31-60	Eu	+	++	>2.2	>0.9	>5	13-25	>40	31-60
203	[illegible]	31-60	Eu	-	++	0-2.2	0-0.9	3-5	13-25	21-40	31-60
204	[illegible]	31-60	Eu	+	++			3-5	13-25	21-40	31-60
205	[illegible]	31-60	Eu	+	++			>5		>40	31-60
206	[illegible]	31-60	Eu	-	+			>5		21-40	>60
207	[illegible]	0-30	Eu	-	-	0-2.2	0-0.9	0-2		0-20	
208	[illegible]	31-60	Hypo	-	-	0-2.2	0-0.9	0-2		0-20	31-60
209	[illegible]	31-60	Eu	-	-			0-2		0-20	>60

Appendix B (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
210	S	31-60	Ba	-	-				5-12	0-20	31-60
211	"	32-60	Ba	-	-			0-2		0-20	31-60
212	E	>60	Ba	+	++	>2.2	>0.9	>5	>25	>40	
213	S*	>60	Ba	-	+	0-2.2		0-2	5-12	21-40	31-60
214	S	31-60	Ba	-	-				5-12	0-20	31-60
215	"	31-60	Ba	-	-				5-12	0-20	
216	"	31-60	Ba	-	-			0-2		0-20	>60
217	"	0-30	Ba	-	-			0-2		0-20	0-30
218	"	31-60	Ba	-	-	0-2.2				0-20	31-60
219	"	31-60	Ba	-	-	0-2.2				0-20	31-60

Appendix 3 (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
220	"	>60	Hypo	-	++				>25	>40	>60
221	"	>60	Hypo	+	++			>5		21-40	0-30
222	"	>60	Hypo	-	+		>0.9		13-25	>40	31-60
223	"	>60	Hypo	+	++				>25	21-40	31-60
224	"	>60	Hypo	+	++	>2.2		>5		>40	31-60
225	"	>60	Hypo	-	++			>5		21-40	
226	"$_2$	>60	Hypo	+	++			>5	>25	>40	>60
227	"$_2$	>60	Hypo	+	++	>2.2	>0.9	3-5		>40	31-60
228	"	0-35	Eu	-	-			0-2			31-60
229	"	>60	Eu	+	++	>2.2	>0.9	3-5	13-25	21-40	0-30

Appendix B (continued)

Gene No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
230	E	>60	Hypo	+	++	>2.2	>0.9	>5	>25	>40	31-60
231	"	31-60	Eu	+	++	>2.2	>0.9	>5	>25	21-40	31-60
232	Dw	31-60	Eu							0-20	31-60
233	"	>60	Eu							>40	0-30
234	"	>60	Eu			>2.2		0-2		21-40	31-60
235	"	>60	Eu							0-20	31-60
236	"	>60	Eu			>2.2		0-2		>40	31-60
237	"	31-60	Eu							0-20	31-60
238	"	>60	Eu								
239	"	>60	Eu	-							

Appendix B (continued)

Case No.	Final Diagnosis	J_1	J_2	J_3	J_4	J_5	J_6	J_7	J_8	J_9	J_{10}
240	[illegible]	0-30	[illegible]								
241	[illegible]	31-60	[illegible]								
242	[illegible]	31-60	[illegible]			>2.2		0-2		0-20	31-60
243	[illegible]	>60	[illegible]	-		>2.2		0-2		0-20	
244	[illegible]	31-60	[illegible]							0-20	31-60

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
156	[illegible]	0-1.0	-	0-100	Nodular	Firm	+			+	
157	[illegible]	0-1.0	+	0-100	Nodular	Hard	+			+	+
158	[illegible]	1.1-10	+	0-100	Nodular	Hard	+		+	+	+
159	[illegible]	0-1.0		101-200	Nodular	Hard				+	+
160	[illegible]	0-1.0	+	101-200	Nodular	Firm	+		+	+	+
161	[illegible]	1.1-10	-			Firm	+	-	-	+	+
162	[illegible]	0-1.0	+	0-100	Nodular	Hard	+	-	-	+	+
163	[illegible]	1.1-10	+	>200	Nodular	Firm				+	+
164	[illegible]		-	0-100	Nodular	Firm	+	-		+	+
165	[illegible]	0-1.0	+	101-200	Nodular	Hard	+	-		+	+

Appendix B (continued)

Case No.	Final diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
166	[illegible]	1.1-10	-	0-100	Nodular	Firm	-	-		-	-
167	[illegible]			201-300	Nodular	Firm	-	+	-	-	-
168	[illegible]	0-1.0	+	101-200	Diffuse	Firm	-			-	-
169	[illegible]	1.1-10	+		Nodular	Firm	-		-	-	-
170	[illegible]	0-1.0		> 300	Nodular	Hard	+	+	-	-	-
171	[illegible]	0-1.0	-	0-100	Nodular	Firm	+			-	-
172	[illegible]	1.1-10	+	101-200	Diffuse	Hard	-	-		-	-
173	[illegible]	1.1-10	+	0-100	Nodular	Firm	-	-	+	-	-
174	[illegible]		+	> 200	Nodular	Hard	-	+		-	-
175	[illegible]	1.1-10	+	>200	Nodular	Hard	-	+		-	-

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
176	H*	1.1-10		0-100	Nodular	Firm	+			+	+
177	H*	0-1.0	+	> 200	Diffuse	Soft	+		+	+	+
178	G*	0-1.0	+	0-100	Nodular	Hard		+		+	+
179	H*	0-1.0	+	101-200	Nodular	Hard		+	+	+	+
180	G*	> 10	+	0-100	Nodular	Hard	+	+	+	+	+
181	H*	> 10	+	> 200	Nodular	Soft		+	+	+	+
182	H	0-1.0	+	0-100	Diffuse	Soft	+	+		+	+
183	H	> 10	+	101-200	Nodular	Firm	+			+	+
184	H*	0-1.0			Nodular	Firm	+			+	+
185	H	0-1.0	+	0-100	Nodular	Firm	+	+	+	+	+

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
186	S	1.1-10		101-200	Diffuse	Soft	+			o	o
187	"	1.1-10	+	101-200	Nodular	Firm	o		o	o	o
188	"	0-1.0	+	101-200	Nodular	Firm	+			o	o
189	"	>10	+	> 200	Diffuse	Soft	o			o	o
190	n_0	>10		> 200	Nodular	Soft	o	+	o	o	o
191	n_0	0-1.0	o	101-200	Diffuse	Soft	o	+		o	o
192	n_0	>10	+	101-200	Nodular	Hard		+		o	o
193	"	0-1.0	o	0-100	Diffuse	Hard	o			o	o
194	n_0	>10	+	> 200	Nodular	Firm	o	+		o	o
195	"	>10	o	> 200	Nodular	Firm		+	o	o	o

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
196	[illegible]	>10	+	>200	Nodular	Hard	-	-		-	-
197	[illegible]	1.2-10	+	>200	Nodular	Soft				-	-
198	[illegible]	0-1.0	+	0-100	Nodular	Hard		+			+
199	[illegible]	0-1.0	+	101-200	Nodular	Hard		+		+	
200	[illegible]	0-2.0		0-100	Nodular	Hard		+	+	+	-
201	[illegible]	1.1-10	-	0-100	Nodular	Firm	-	-	-	-	-
202	[illegible]	1.1-10	-	101-200	Nodular	Firm	-	+	-	-	-
203	[illegible]	1.1-10	-	0-100	Nodular	Firm	-	+	-	-	-
204	[illegible]	1.1-10	-	0-100	Nodular	Firm	-	+	-	-	-
205	[illegible]	1.1-10	-	0-100	Nodular	Firm	-	+	-	-	-

Appendix 3 (continued)

Core No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
206	H*	1.1-10	+	101-200	Mottled	Firm	-	+	-	-	-
207	S	1.1-10	-	0-100	Nodular	Soft	-	+	-	-	-
208	S	0-1.0	+	0-100	Nodular	Soft	-	-	-	-	-
209	S	0-1.0	+	0-100	Nodular	Soft	-	+	-	-	-
210	S	1.1-10	-	101-200	Mottled	Soft	-	+	-	-	-
211	S	>10	-	101-200	Nodular	Soft	-	+	-	-	-
212	S	1.1-10	-	101-200	Nodular	Hard	-	+	-	-	-
213	S*	0-1.0	+	0-100	Nodular	Hard	+	+	+	+	+
214	S	1.1-10	-	101-200	Diffuse	Soft	+	+	-	-	-
215	S	1.1-1.0	+	201-300	Diffuse	Soft	-	+	-	-	-

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
216	S	0-1.0	+	0-100	Diffuse	Soft	-	+	-	-	-
217	"	1.1-10	+	0-100	Diffuse	Soft	-	+	-	-	-
218	"	1.1-10	+	0-100	Nodular	Soft	+	-	-	-	-
219	"	1.1-10	-	101-200	Nodular	Firm	-	+	-	-	-
220	"	0-1.0	+	0-300	Nodular	Firm	+	+	-	-	-
221	"	0-1.0	-	0-100	Diffuse	Firm	-	+	-	-	-
222	"	1.1-10	+	0-100	Nodular	Firm	+	+	-	-	-
223	"	1.1-10	+	0-300	Diffuse	Firm	+	+	-	-	-
224	"	1.1-10	-	0-100	Nodular	Firm	+	+	-	-	-
225	"	0-1.0	-	0-300	Diffuse	Firm	-	-	-	-	-

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
226	[illegible]	1.1-10	-	0-100	Diffuse	Firm	-	+	-	-	-
227	[illegible]	1.1-10	+	0-100	Nodular	Firm	+	-	-	-	-
228	[illegible]	1.1-10	-	0-100	Diffuse	Soft	-	-	-	-	-
229	[illegible]	1.1-10	+	0-100	Nodular	Firm	-	+	-	-	-
230	[illegible]	1.1-10	-	101->200	Diffuse	Hard	-	+	-	-	-
231	[illegible]	1.1-10	-	0-100	Nodular	Firm	-	+	-	-	-
232	[illegible]	>10	-	0-100	Nodular	Firm	-	-	-	-	+
233	[illegible]	0-1.0	+		Nodular	Firm		+	-	+	+
234	[illegible]	0-1.0	+	0-200		Hard		+		+	+
235	[illegible]	0-1.0	+	0-100	Nodular	Firm	-	-	-	-	+

Appendix B (continued)

Case No.	Final Diagnosis	J_{11}	J_{12}	J_{13}	J_{14}	J_{15}	J_{16}	J_{17}	J_{18}	J_{19}	J_{20}
236	[illegible]	0-1.0	-	0-100	Nodular	Hard	+	+	+	+	-
237	[illegible]	0-1.0	+			Hard	-			+	+
238	[illegible]	0-1.0	+	0-100	Nodular	Hard	+	+		+	+
239	[illegible]	0-1.0	-		Nodular	Hard	-	+		+	-
240	[illegible]	0-1.0	+	0-100	Diffuse	Firm			-	-	-
241	[illegible]	1.1-3.0	+	101-200	Nodular	Firm	-	+		-	-
242	[illegible]	0-1.0	+	> 200	Nodular	Hard	-	+		-	+
243	[illegible]	0-1.0	+		Nodular	Hard	+			+	+
244	[illegible]	0-1.0	+	> 200	Nodular	Hard		+		+	+

Appendix D (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
156	[illegible]		0-0.20				-	-	-	-	
157	[illegible]		0-0.20			-	-	-	-	-	-
158	[illegible]		1.00	80-100		-	-	-	-		
159	[illegible]		0.21-1.00	0-79		-			-		+
160	[illegible]		1.00			-	-	-	-		
161	[illegible]		0-0.20			-	-	-	-	+	-
162	[illegible]		0.21-1.00	0-79		-	-	-	-	+	-
163	[illegible]		0.21-1.00	0-79		-	-	-	+	+	+
164	[illegible]		0.21-1.00			-	-	-	-	-	-
165	[illegible]		0.21-1.00	80-100		-	-	+	-	+	-

Appendix B (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
166	"	3.1-5.0	0-0.20			-	-	-	-	-	-
167	"		0-0.20			-	-	+	-	-	-
168	"		0.21-1.00	0-79		+	-	-	-	-	-
169	"		0.21-1.00			-	-	+	+	+	-
170	"		0.21-1.00	0-79		+	+	-	-	-	
171	"		0.21-1.00				-	-	-	-	-
172	"		0-0.20		+	-	-	-	+	+	-
173	"		0-0.20			-	-	+	+	+	-
174	"		0.21-1.00	0-79	+	+	+		-	-	
175	"		0-0.20				-	-	+	-	

Appendix 3 (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
176	[illegible]		0.21-1.00	0-79		-	-	-	-	-	-
177	[illegible]		> 1.00	0-79		-	-	-	-	-	-
178	[illegible]		0-0.20			-	+	+	+	+	+
179	[illegible]					-	-	+	+	+	+
180	[illegible]		0-0.20			-	-	-	-	-	+
181	[illegible]		0-0.20			-	-	+	-		+
182	[illegible]		0-0.20			-	-	-	-	-	-
183	[illegible]					-	-	-	-	+	-
184	[illegible]		0-0.20			-	-	-	-	-	-
185	[illegible]	0-3.0	0-0.20		+	-	-	-	-	-	-

Appendix B (continued)

Core No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
186	S		0-0.20			-	-	-	-		
187	"		0-0.20			-	-	-	-	-	-
188	"					-	+	+	+	-	-
189	"		0-0.20			-	-	-	+	+	-
190	"		0-0.20			-	-	-	+	+	-
191	"		0-0.20			-	-	-	-	+	-
192	"		0-0.20			-	-	-	-	+	-
193	"		0-0.20			-	-	-	-	-	-
194	"		0-0.20				-	-	-	-	-
195	"		0-0.20			-	-	-	-	-	-

Appendix B (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
196	"		0-0.20			-	-	-	-	-	-
197	"		0-0.20				-	-	-	-	+
198	"		0-0.20			-	+	+	-		
199	"					-		+	+	+	+
200	"		0-0.20					+	+	+	+
201	II	3.1-5.0	>1.00		+	+	-	-	-	-	-
202	"	3.1-5.0	>1.00			-	-	-	-	+	-
203	"	3.1-5.0	>1.00			-	-	-	-	-	-
204	"	3.1-5.0	0.21-1.00			-	-	-	-	+	-
205	"	3.1-5.0	>1.00		+	+	-	-	-	+	-

Appendix B (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
206	B*	3.1-5.0	0.21-1.00			-	-	-	-	+	-
207	S	3.1-5.0	0-0.20			-	-	-	-	+	-
208	"	3.1-5.0	0.0-20			-	-	-	-	-	-
209	S	3.1-5.0	0-0.20			-	-	-	-	+	-
210	"	3.1-5.0	0-0.20			-	-	-	-	+	-
211	"	3.1-5.0	0-0.20			-	-	-	+	+	-
212	B	0-3.0	>1.00			+	-	+	+	+	-
213	G*	3.1-5.0	0.21-1.00			-	+	+	+	+	+
214	S		0-0.20			-	-	-	-	+	-
215	"	3.1-5.0	0-0.20			-	-	-	+	+	-

Appendix D (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
216	S	3.1-5.0	0-0.20			-	-	-	-	+	-
217	"		0-0.20			-	-	-	-	+	-
218	"		0-0.20			-	-	-	+	+	-
219	H	3.1-5.0	0.21-1.00		+	-	-	+	-	+	-
220	"	0-3.0	0.21-1.00			-	+	+	-	-	+
221	"	0-3.0	0.21-1.00			-	-	+	+	+	+
222	"		0.21-1.00			-	-	-	+	-	-
223	"	0-3.0	0.21-1.00			-	-	-	+	+	+
224	"	0-3.0	0.21-1.00			-	+	+	+	+	+
225	"	0-3.0	>1.00		+	-	-	+	+	+	+

Appendix B (continued)

Case No.	Final Diagnosis	J_{21}	J_{22}	J_{23}	J_{24}	J_{25}	J_{26}	J_{27}	J_{28}	J_{29}	J_{30}
226	"	0-3.0	> 1.00			-	-	-	+	+	+
227	"	0-3.0	0.21-1.00		+	-	+	+	+	+	+
228	"	3.1-5.0	0-0.20			-	-	-	-	-	-
229	"	0-3.0	0.21-1.00				-	-	-	+	-
230	"	3.1-5.0	0.21-1.00		-	-	-	-	-	+	-
231	"	3.1-5	> 1.00		+	-	-	-	-	+	-
232	"		0-0.20			-	-	-	-	-	-
233	"		0.21-1.00			-	-	-	-	-	-
234	"		0-0.20			-		+			
235	"		0-0.20			-	-	-	-	-	-

Appendix 3 (continued)

Gene No.	Final Diagonals	δ_{21}	δ_{22}	δ_{23}	δ_{24}	δ_{25}	δ_{26}	δ_{27}	δ_{28}	δ_{29}	δ_{30}
235	D^{*}		0-0.20				-	+	+	+	-
237	D_2		0-0.20			-	-	-	-	-	-
238	D_2					-	+	-	+	-	-
239	D_2						-	-	-	-	-
240	D_2					-	-	-	-	-	-
241	D_2			1.00		-	-	-	-	+	-
242	D_2	>5.0	0.21-1.00			-	-	+	-	-	-
243	D_2					-	-	-	-	-	-
244	D_2		0.21-1.00	80-100			+	+			+

80-100

APPENDIX C

The Computer Programme for the Identification of Thyroid Disease.

```
::PROGRAMME FOR ASSISTING IN THE IDENTIFICATION OFTHYROID DISEASE
SETS M(31)U(30)S(40)NTVIJKLR(90)QCZH(40)GEF
SETV B(80)W(1000)PAXDY(30)
SETF PUNCH
SETR 320
100)OUTPUT 27
OUTPUT 29
OUTPUT 30
WAIT
JUMP @Z
163)PUNCH 1
JUMP @165
164)TELEPRINTER
JUMP @165
62)@
700:032,
42163):40164)
000:200
)
165)READ N::NO. OF DISEASES
JUMP UNLESS N%40@61
OUTPUT 31::N%40,PRINT N AND RAREAD
OUTPUT 14
Z=62
JUMP @100
61)READ T::NO. OF SYMPTOMS AND TESTS
JUMP UNLESS T%30@42
OUTPUT 31::T%30,PRINT T AND REREAD
OUTPUT 20
Z=61
JUMP @100
42)READ M(31)::0 IF REL.LIKLIHOOD,1 IF BAYESIAN PROBS. BEING USED

144)V=0
VARY I=0:1:T
83)READ M(I)::NO. OF POSSIBLE RESULTS FORTEST I
V=V+M(I)
REPEAT I
READ M(30)::SUMCHECK
JUMP IF M(30)=V@41
OUTPUT 31::SUMCHECK FAILURE
OUTPUT 13::PRINT M AND REREAD
Z=42
JUMP @100
41)K=0::WEIGHTS READ IN BY ROWS, EACH ROW SUMCHECKED
99)VARY I=0:1:T
V=N*M(I)
```

```
44)X=0
VARY J=K:1:V
READ W(J)
X=X+W(J)
REPEAT J
READ W(1000)
X=W(1000)-X
X=MOD X
JUMP IF X$0.00002@43
OUTPUT 31::W ROW SUMCHECK FAILURE, PRINT ROW NO. AND REREAD ROW
OUTPUT 23
OUTPUT 27
PRINT I
Z=44
JUMP @100
43)K=K+V
66)REPEAT I
@
700:032,
4292):40166)
000:020
)
166)TITLE
THE DISEASES AMONGST WHICH IT IS ASSUMED THAT THE UNKNOWN
IS TO BE FOUND ARE :


CYCLE I=1:1:N::PRINT LIST OF DISEASES IN SET
SUBR I
LINES 1
REPEAT I
TITLE
THE SYMPTOMS AND TESTS BEING CONSIDERED ARE :


CYCLE I=1:1:T::PRINT LIST OF TESTS IN SET
J=I+101
SUBR J
LINES 1
REPEAT I
92)READ Q::PARAMETER TO INDICATE NEW RUN OR CONTINUATION
JUMP UNLESS Q=0@45
98)VARY J=0:1:T
S(J)=-1::NEW RUN
REPEAT J
97)VARY K=0:1:N
B(K)=1.0
B(K+41)=1.0
REPEAT K
JUMP @52
45)Q=0::VALUE OF Q DESTROYED
```

```
VARY J=0:1:T
READ S(J)::CONTINUATION OF PREVIOUS RUN
Q=Q+S(J)
REPEAT J
READ S(30)
JUMP IF S(30)=Q@47
OUTPUT 31::S SUMCHECK FAMLURE, PRINT S AND REREAD S(J)
Z=45
JUMP @100
47)C=0
139)X=0
VARY K=C:1:N
READ B(K)
X=X+B(K)
REPEAT K
READ B(40)
X=B(40)-X
X=MOD X
JUMP IF X$0.0000041@64
OUTPUT 31::B SUMCHECK FAILURE, PRINT B AND REREAD B(K)
OUTPUT 2
Z=47
JUMP @100
64)JUMP UNLESS C=0@161
C=41
JUMP @139
161)Q=0
VARY K=0:1:T
READ R(K)
Q=Q+R(K)
REPEAT K
READ R(90)
JUMP IF R(90)=@52
TITLE R(K) SUMCHECK FAILIURE
Z=161
JUMP @100
52)READ Q::NO. OF TEST/RESULT PAIRS
V=0
C=-1
96)VARY I=0:1:Q
48)READ K::TEST NUMBER
READ R(K)::RESULT FOR TEST K
JUMP UNLESS K%T-1@49
OUTPUT 31
OUTPUT 11::K OUT OF RANGE
JUMP @51
49)JUMP UNLESS R(K)%M(K)-1@50
OUTPUT 31
OUTPUT 18::R(K) OUT OF RANGE
51)Z=48
JUMP @100::REREAD K,R(K)
```

```
50)JUMP UNLESS K$C@53::CHECK TEST NOS. IN ORDER
OUTPUT 31::OUT OF ORDER, PRINT C
OUTPUT 3::AND REREAD
JUMP @51
53)JUMP IF K=C+1@54
C=C+1
K=K-1
L=0
95)CYCLE J=C:1:K
L=L+M(J)
REPEAT J
L=L*N
V=V+L
K=K+1
54)V=V+R(K)
S(K)=1
J=N-1
94)CYCLE L=0:1:J
B(L)=W(V)*B(L)
V=V-R(K)
F=M(K)-1
A=W(V)
VARY Z=V:1:F


JUMP IF A%W(Z+1)@63
A=W(Z+1)
63)REPEAT Z
B(41+L)=A*B(41+L)
V=V+R(K)
V=V+M(K)
REPEAT L
V=V-R(K)
C=K
REPEAT I
TITLE
```

IDENTIFICATION:

```
GIVEN:


F=167
VARY K=0:1:T
JUMP IF K=0@132
F=F+M(K-1)
132)JUMP UNLESS SK=1@90
K=K+102
SUBR K
K=K-102
```

```
SUBR F
LINES 2
90)REPEAT K

86)READ P::DISCRIMINATION LEVEL ON DISEASES
READ F::OUTPUT LIMIT ON DISEASES
JUMP IF M31=0@138
TITLE
(N.B. FOR 'RELATIVE LIKELIHOOD' BELOW, READ ''BAYESIAN PROBABILITY


138)TITLE THEN APPLYING THESE RESULTS TO THE COMPLETE SET OF DISEA
                                                                SES,
JUMP IF F=0@89
JUMP IF P=0@88
TITLE THE MOST LIKELY ARE,IN ORDER OF PREFERENCE
(TAKING EITHER THE FIRST
PRINT F,2
TITLE  OR THOSE WHOSE
% RELATIVE LIKELIHOOD IS GREATER THAN
A=P*100
PRINT A,3:0
TITLE  %, WHICHEVER IS LEAST):
JUMP @55
89)JUMP IF P=0@87
TITLE THE MOST LIKELY ARE,I
ORDER OF PREFERENCE
(TAKING THOSE WHOSE % RELATIVE LIKELIHOOD IS GREATER THAN
A=P*100
PRINT A,3:0
TITLE ):
JUMP @55
88)TITLE THE
PRINT F,2
TITLE  MOST LIKELY ARE,IN ORDER OF PREFERENCE :
JUMP @55
87)TITLE P AND F BOTH ZERO
WAIT
JUMP @86::REREAD P AND F
55)LINES 2
@
700:032,
42145):40146)
000:100
)
146)TITLE                                        REL.LIKEL.(%)
@
700:41145)
)
TITLE    FRAC.OPT.PAT.
145)LINES 2
```

```
 JUMP UNLESS C=0@92
 C=41
 JUMP @101
 162)R(30)=0
 VARY K=0:1:T
 PRINT R(K),2
 R(30)=R(30)+R(K)
 REPEAT K
 PRINT R(30),4
 WAIT
 JUMP @92

 72)TITLE
  NO FURTHER SYMPTOMS AND TESTS

 WAIT
 JUMP @92::START NEW RUN
 76)TITLE
  ONLY ONE DISEASE

 WAIT
 JUMP @92::START NEW RUN
 59)TITLE
 ALL DISEASES ELIMINATED

 WAIT
 84)D=0
 VARY K=0:1:N
 D=D+BK
 REPEAT K
 JUMP @78
 JUMP @92
```

```
1)TITLE   HASHIMOTO'S DISEASE
EXIT
2)TITLE   NON-TOXIC GOITRE
EXIT
3)TITLE   THYROID CANCER
EXIT
102)TITLE  PRECIPITIN TEST
EXIT
103)TITLE  SERUM GLOBULINS
EXIT
104)TITLE  DISCOMFORT
EXIT
105)TITLE  TRACHEAL DEV. OR
COMP. ON X-RAY
EXIT
106)TITLE  LARYGEAL PALSY
EXIT
107)TITLE  FIXATION TO TISSUES
EXIT
108)TITLE  CERVICAL LYMPH NODES
EXIT
109)TITLE  PYRAMIDAL LOBE
EXIT
110)TITLE  PAIN IN GOITRE
EXIT
111)TITLE  HOARSENESS
EXIT
112)TITLE  DYSPHAGIA
EXIT
113)TITLE  CHOKING OR TIGHTNESS
EXIT
114)TITLE  COUGH OR STRIDOR
EXIT
115)TITLE  KCLO4 DISCHARGE
EXIT
116)TITLE  RECENT INCREASE IN SIZE
EXIT
117)TITLE  NODULAR OR DIFFUSE
EXIT
118)TITLE  BE131I
EXIT
119)TITLE  GAMMAGLOBULIN
EXIT
120)TITLE  E.S.R.
EXIT
121)TITLE  24-HR. THYROIDAL
131I UPTAKE
EXIT
```

```
122)TITLE  PB127I
EXIT
123)TITLE  PB131I AT 48 HOURS
EXIT
124)TITLE  DURATION(YEARS)
EXIT
125)TITLE  ESTIMATED SIZE
OF GLAND(GRAMS)
EXIT
126)TITLE  CONSISTENCY
EXIT
127)TITLE  CLINICAL STATUS
EXIT
128)TITLE  C.F.T.
EXIT
129)TITLE  THYMOL TURBIDITY
EXIT
130)TITLE  ZNSO4 TURBIDITY
EXIT
131)TITLE  AGE
EXIT
167)TITLE  +
EXIT
168)TITLE  -
EXIT
169)TITLE  0-2.2
EXIT
170)TITLE  2.3-
EXIT
171)TITLE  NO
EXIT
172)TITLE  YES
EXIT
173)JUMP @171
174)JUMP @172
175)JUMP @171
176)JUMP @172
177)JUMP @171
178)JUMP @172
179)TITLE  IMPALPABLE
EXIT
180)TITLE  PALPABLE
EXIT
181)TITLE  ABSENT
EXIT
182)TITLE  PRESENT
EXIT
183)JUMP @171
184)JUMP @172
185)JUMP @171
186)JUMP @172
```

```
187)JUMP @171
188)JUMP @172
189)JUMP @171
190)JUMP @172
191)JUMP @171
192)JUMP @172
193)JUMP @167
194)JUMP @168
195)JUMP @172
196)JUMP @171
197)TITLE  NODULAR
EXIT
198)TITLE  DIFFUSE
EXIT
199)TITLE  0-79%
EXIT
200)TITLE  80-100%
EXIT
201)TITLE  0-0.9
EXIT
202)TITLE  1.0+
EXIT
203)TITLE  0-20
EXIT
204)TITLE  21-40
EXIT
205)TITLE  41+
EXIT
206)TITLE  0-30
EXIT
207)TITLE  31-60
EXIT
208)TITLE  61+
EXIT
209)TITLE  0-3
EXIT
210)TITLE  3.1-5
EXIT
211)TITLE  5.1+
EXIT
212)TITLE  0-0.20
EXIT
213)TITLE  0.21-1
EXIT
214)TITLE  1.01+
EXIT
215)TITLE 0-1
EXIT
216)TITLE  1.1-10
EXIT
217)TITLE  10.1+
```

```
151)VARY J=0:1:T  :NOTE THOSE PRINTED
JUMP IF F=0@73
JUMP IF J%F=1@71
73)K=U(J)+102
A=Y(K-102)/Y(E)
JUMP IF P=0@65
JUMP IF A$P@71
65)JUMP IF A=0@71
SUBR K
@
700:032,
42149):40150)
000:100
)
150)OUTPUT 0
OUTPUT 27
PRINT A,1:4
149)LINES 2
71)REPEAT J
JUMP IF F=0@91
JUMP UNLESS P=0@91
JUMP UNLESS A=0@91
TITLE
NO OTHER DISCRIMINATING SYMPTOMS OR TESTS FOR THIS SET OF DISEASES

91)WAIT
@
700:032,::READ HANDSWITCHES,
4252):4056)::F2=0 MEANS CONTINUE
000:010::F2=1 MEA NEW RUN

)
56)VARY K=0:1:30::ENABLING PREVIOUS RUN TO CONTINUE LATER
OUTPUT 0
REPEAT K
Q=1
PRINT Q,4
S(30)=0
VARY J=0:1:T
LINE

PRINT S(J),4
S(30)=S(30)+S(J)
REPEAT J
LINE
PRINT S(30),4
C=0
101)B(40)=0.0
VARY I=C:1:N
PRINT B(I),9/
B(40)=B(40)+B(I)
LINE
REPEAT I
PRINT B(40),9/
```

```
CHECK U(J)
CHECK Y(L)
REPEAT J
82)VARY J=0:1:T
Y(J)=-Y(J)-1.0::RESTORE Y(J)
CHECK Y(J)
REPEAT J::SORTING COMPLETA
LINE
E=U(0)
JUMP IF Y(E)=0@72
46)READ P::DISCRIM. LEVEL ON TESTS
READ F::OUTPUT LIMIP ON TESTS
JUMP IF F=0@81
JUMP IF P=0@80
TITLE THE BEST SYMPTOMS AND TESTS FOR DISTINGUISHING BETWEEN THESE
ARE,IN ORDER OF PREFERENCE(TAKING EITHER THE FIRST

PRINT F,2
TITLE
OR THOSE WHOSE POWER IS GREATER THAN
PRINT P,1:2
TITLE  OF THE MAXIMUM
POWER SCORED, WHICHEVER IS LEAST):
JUMP @79
81)JUMP IF P=0@60
TITLE THE BEST SYMPTOMS AND TESTS FOR DISTINGUISHING BETWEEN THESE
ARE,IN ORDER OF PREFERENCE(TAKING THOSE WHOSE POWER IS GREATER
THAN
PRINT P,1:2
TITLE  OF THE MAXIMUM POWER SCORED ):
JUMP @79
80)TITLE THE
PRINT F,2
TITLE  BEST SYMPTOMS AND TESTS FOR DISTINGUISHING BETWEEN THESE
ARE,IN ORDER OF PREFERENCE:

JUMP @79
60)TITLE P AND F BOTH ZERO
WAIT
JUMP @46::REREAD P AND F
79)LINES 2
@
700:032,
42151):40152)
000:100
)
152)TITLE                              REL.DISCR.POWER
```

```
VARY I=0:1:N::SORTING
L=0
:C=N-1
93)VARY K=0:1:C
JUMP IF B(K+1)%B(L)@57::FIND MAX. B(K)
JUMP @58
57)L=K+1
58)REPEAT K
H(I)=L
JUMP UNLESS B(L)=0@141
B(L)=2.0
141)B(L)=-B(L)
:CHECK H(I)
:CHECK B(L)
REPEAT I
VARY K=0:1:N
JUMP UNLESS B(K)=-2.0@142
B(K)=0
142)B(K)=-B(K)
REPEAT K
E=H(0)
JUMP IF B(E)=0@59
JUMP UNLESS M31=0@84
:D=B(E)
:78)VARY I=0:1:N
K=H(I)+1
A=B(K-1)/D
JUMP IF P=0@77
JUMP IF A$P@85

JUMP IF F=0@74
:77)JUMP IF I%F-1@85
74)SUBR K::PRINT DISEASE NAME
@
:700:032,
42147):40148)
000:100
)
148)OUTPUT 0
OUTPUT 27
A=A*100.0::LIKELIHOOD RATIO AS %
PRINT A,3:6
@
:700:41147)
)
A=B(K-1)/B(K+40)::OPTIMUM
PRINT A,3:6
147)LINES 2
B(K-1)=-B(K-1)::NOTE THOSE PRINTED
85)REPEAT I
```

```
I=0::FORM LIST OF RELEVANT DISEASES
VARY K=0:1:N
JUMP UNLESS B(K)$0@67
H(I)=K
B(K)=-B(K)
:CHECK H(I)
I=I+1
67)REPEAT K
Z=I-1
JUMP IF Z=0@76::ONLY ONE DISEASE
VARY J=0:1:T
Y(J)=0
JUMP UNLESS S(J)=-1@68
G=0
JUMP IF J=0@75
VARY I=0:1:J
G=G+M(I)
REPEAT I
:75)G=G*N
:CHECK G
E=Z-1
:CYCLE L=0:1:E
F=L+1
:CYCLE C=F:1:Z
VARY K=0:1:M(J)
I=M(J)*H(L)
I=G+I
W(1000)=W(I+K)
I=M(J)*H(C)
I=G+I
W(1000)=W(1000)-W(I+K)
W(1000)=MOD W(1000)
Y(J)=Y(J)+W(1000)
REPEAT K
REPEAT C
REPEAT L
68)I=I::WASTE TO ENABLE ALL Y(J) TO BE CHECKED
:CHECK Y(J)
REPEAT J
VARY J=0:1:T::SORT Y(J) INDICES
L=0
:C=T-1
VARY K=0:1:C
JUMP IF Y(K+1)%Y(L)@69
JUMP @70
69)L=K+1
:70)REPEAT K
U(J)=L

Y(L)=-Y(L)-1.0
```

```
EXIT
218)TITLE  0-100
EXIT
219)TITLE  101-200
EXIT
220)TITLE  201+
EXIT
221)TITLE  FIRM
EXIT
222)TITLE  HARD
EXIT
223)TITLE  SOFT
EXIT
224)TITLE  HYPOTHYROID
EXIT
225)TITLE  EUTHYROID
EXIT
226)TITLE  HYPERTHYROID
EXIT
227)TITLE  ++
EXIT
228)JMP @167
229)JMP @168
230)TITLE  0-2
EXI
231)TITLE  3-5
EXIT
232)TITLE  6+
EXIT
233)TITLE  5-12
EXIT
234)TITLE  13-25
EXIT
235)TITLE  26+
EXIT
236)TITLE  0-30
EXIT
237)TITLE  31-60
EXIT
238)TITLE  61+
EXIT
START 62
```